Chapter 94: Diabetes Mellitus

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UPDATE SUMMARY

Update Summary

May, 2023

The following sections, tables, and figures were updated:

- Extensive revisions were made throughout the chapter based on the new recommendations from the 2023 American Diabetes Association Standards of Care to the following sections:
  - Approach to treatment
  - Stepwise addition of medications
  - Complications and comorbidities
- Tirzepatide, a dual glucose-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, was approved by the FDA in 2022. Information regarding tirzepatide has been added in multiple sections and Table 94-10.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 19, Diabetes Mellitus.

KEY CONCEPTS

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1 Diabetes mellitus (DM) is a metabolic disorder. While there are numerous etiological causes, defects in insulin secretion, insulin action (sensitivity), or both lead to elevations in blood glucose as well as altered fat and protein metabolism.

2 DM is a leading cause of eye and kidney disease. Patients with DM are at high risk for CV events, heart failure, and atherosclerotic disease.

3 The two most common classifications of DM are type 1 (absolute insulin deficiency) and type 2 (relative insulin deficiency due to β-cell dysfunction coupled with insulin resistance). They differ in clinical presentation, pathophysiology, and treatment approach.

4 The prevalence of type 2 DM has doubled worldwide over the last 40 years. This has been attributed to an alarming increase in the prevalence of obesity due to diminished physical activity and increased caloric consumption.

5 The diagnosis of diabetes is made using any of the following criteria: (1) fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L); (2) a

hemoglobin A1C (A1C) ≥6.5% (0.065; 48 mmol/mol); (3) a random plasma glucose level ≥200 mg/dL (11.1 mmol/L) coupled with classic symptoms of diabetes; or (4) a 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test (OGTT). A diagnosis using criteria 1-3 requires two abnormal test results from the same sample or in two separate test samples.

6 The goals of therapy in DM are to achieve optimal glycemic control (based on age, comorbid conditions, and patient preferences), reduce the onset and progression of diabetes-related complications, aggressively address CV risk factors, and improve quality of life.

7 Intensive glycemic control prevents the onset and slows the progression of microvascular complications (eg, neuropathy, retinopathy, and nephropathy).

8 Knowledge of the patient's meal patterns and activity levels, as well as the pharmacologic properties of antihyperglycemic agents, is essential to creating an individualized treatment plan that achieves optimal glycemic control, avoids hypoglycemia, and minimizes adverse effects.

9 Metformin has historically been used as the initial treatment for most patients with type DM. However, sodium-glucose transporter-2 (SGLT2) inhibitors and some glucagon-like peptide -1 (GLP-1) receptor agonists have well-established benefits in specific patient populations. Several guidelines now recommend a person-centered approach when selecting the initial treatment taking into consideration cardiovascular and kidney benefits, glucose-lowering efficacy, impact on weight, cost, and adverse effects.

10 Type 2 DM often requires the use of multiple therapeutic agents (combination therapy) including oral and injected antihyperglycemics to achieve and maintain optimal glycemic control. A persistent decline in β-cell function over time often necessitates periodic adjustment and changes in therapy.

11 Insulin therapy is required in type 1 DM. Intensive basal-bolus insulin therapy, either via multiple daily injections of insulin or continuous subcutaneous insulin infusion therapy (aka an insulin pump), in motivated individuals is more likely to achieve optimal glycemic control. Basal-bolus therapy includes a long-acting insulin to address fasting glucose and a rapid-acting insulin for mealtime coverage. The use of adjunctive therapy in combination with insulin in patients with uncontrolled or erratic glucose concentrations may be warranted.

12 Aggressive management of CV risk factors in DM is necessary to reduce the incidence of CV events and death. This includes smoking cessation, use of moderate or high potency statins in most patients with DM, and treatment of hypertension.

13 Good blood pressure control in patients with diabetes lowers not only the risk of retinopathy and nephropathy but also CV events.

14 Strategies to prevent type 1 DM have not yet been successful. For patients at high risk, type 2 DM can be delayed or prevented by engaging in regular aerobic exercise, losing weight, reducing dietary fat, and increasing fiber intake. These lifestyle habits can reduce the risk of type 2 DM by 60%. Although no medication is currently FDAapproved to prevent diabetes, several have been shown to delay diabetes onset in high-risk patients.

15 Repeated inaction by practitioners to intensify treatment when patients are not meeting treatment goals is called therapeutic inertia. Several factors contribute to therapeutic inertia. This is a common problem and among the leading contributors to poor outcomes. Diabetes is a chronic condition that requires periodic medication changes to attain and maintain glycemic goals.

16 Patient self-management, therapeutic lifestyle behaviors, and appropriate medication use are equally important components of each patient's treatment plan. Interprofessional teams including physicians (primary care, endocrinologists, ophthalmologists), dentists, dietitians, nurses, pharmacists, podiatrists, social workers, behavioral health specialists, and certified diabetes care and education specialists (CDCESs) working together can assist persons with DM in achieving optimal health outcomes.

BEYOND THE BOOK

BEYOND THE BOOK

Part 1:

Donna is a 53-year-old woman with a 5-year history of type 2 DM. She also has dyslipidemia and hypertension. She has atherosclerotic cardiovascular disease with two coronary artery stents placed 1 year ago. She has gained 5 lb (2.3 kg) in the last 6 months. She takes metformin 1,000 mg by mouth twice daily for type 2 DM. Her most recent laboratory results include: A1C 8.1% (0.081; 65 mmol/mol), eGFR >60 mL/min/1.73 m^2, UACR 14 mg/g (1.6 mg/mmol). She wants to lose weight and has commercial insurance. The patient's nurse practitioner wrote a prescription for insulin glargine U-100 10 units SC once daily.

Find the current diabetes treatment guidelines from both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE). Is this treatment approach in Donna's case consistent with the guidelines? If it is, explain why. If it is not, determine what would be recommended instead and explain why.

Part 2:

Assume that the prescription for insulin glargine is appropriate. Review the following resource on how to inject insulin.

Find two additional resources that you could use when educating Donna on this new prescription. How did you find them? How did you determine the resource was from a reputable and reliable source? What are the key components you should discuss with this patient about the proper use of insulin?

INTRODUCTION

1 2 Diabetes mellitus (DM) is a diverse group of metabolic disorders that all have chronically elevated blood glucose (BG) as their defining feature. In addition to hyperglycemia, DM is associated with abnormal fat and protein metabolism. In the absence of effective treatment, DM can lead to acute complications such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS). Chronic hyperglycemia can cause vascular and nerve damage, resulting in microvascular, macrovascular, and neuropathic complications. DM is a worldwide problem, significantly impacting people and healthcare systems in low-, middle-, and high-income countries.[1] More than 442 million adults around the globe are now living with DM, and its prevalence has nearly doubled over the last 30 years. According to the Centers for Disease Control and Prevention, slightly more than 34 million Americans, including 13% of adults, have DM.[2] While 1.5 million new cases of DM are diagnosed in the United States every year, one in four Americans with DM are unaware they have it. While these numbers are startling, the number of adults with prediabetes is far greater—an estimated 88 million in the United States alone. Prediabetes is a condition of abnormal BG that is not sufficiently high to meet the thresholds that define diabetes but often progresses to the diagnosis. The total direct and indirect medical costs for treating people with DM in the United States were $327 billion in 2017.[3] The average person with DM spent $16,750 in 2017 on medical care, an amount that was nearly two-and-half times greater than the amount spent by people without DM. DM is the seventh leading cause of death in the United States and among the principal causes of end-stage kidney disease (ESKD), lower extremity amputations, and blindness. Finally, people with DM are at far greater risk for CV disease (eg, myocardial infarction, ischemic stroke).[2] Optimal management of DM substantially lowers the risk of complications, increases life expectancy, and improves the quality of life.

EPIDEMIOLOGY

3 The vast majority of patients with DM are classified into one of two broad categories: type 1 DM and type 2 DM.[4] Patients with type 1 DM have an absolute insulin deficiency. Patients with type 2 DM have varying degrees of β-cell dysfunction often coupled with insulin resistance. Women who develop diabetes during pregnancy are classified as having gestational diabetes (GDM). Less common types of diabetes are caused by genetic defects, pancreatic destruction, endocrine disorders, and medications. See Table 94-1.

TABLE 94-1

Classification of Diabetes Mellitus

Type 1 diabetes[a] (immunologically mediated destruction of β-cells leading to absolute insulin deficiency)
Type 2 diabetes (progressive loss of β-cell insulin secretory function accompanied by resistance to insulin action)
Gestational diabetes mellitus
Monogenic defects
Maturity-onset diabetes of the young (MODY) caused by a mutation in GCK, HNF1A, HNF1B, or HNF4A gene
Neonatal diabetes caused by a mutation in KCNJ11, ABCC8, INS, GATA6, EIF2AK3, or FOXP3 gene
Genetic syndromes associated with diabetes
Down syndrome
Hemochromatosis
Klinefelter syndrome
Turner syndrome
Diseases impacting the pancreas leading to diabetes
Cystic fibrosis
Pancreatitis
Pancreatic cancer
Pancreatectomy
Posttransplantation diabetes mellitus
Endocrine diseases frequently associated with diabetes
Acromegaly
Aldosteronoma
Cushing syndrome
Glucagonoma

Hyperthyroidism
Pheochromocytoma
Somatostatinoma
Medication-induced hyperglycemia[5]
Atypical antipsychotics (eg, risperidone, olanzapine)
β-Blockers (eg, propranolol, atenolol)
β-Adrenergic agonists (eg, albuterol)
Calcineurin inhibitors (eg, cyclosporine, tacrolimus)
Diazoxide
Gatifloxacin
Glucocorticoids (eg, dexamethasone, prednisone)
Growth hormone (rhGH)
HMG-CoA reductase inhibitors (eg, atorvastatin, simvastatin)
Niacin/nicotinic acid
Pentamidine
Protease inhibitors (eg, ritonavir, saquinavir)
Thiazide diuretics (eg, chlorthalidone, hydrochlorothiazide)

[a]Patients with any form of diabetes may require insulin treatment at some stage of their disease. Insulin use does not itself classify the type of diabetes.

Data from Reference 4.

Type 1 DM accounts for 5% to 10% of all cases of DM and is most often due to autoimmune destruction of the pancreatic β-cells.[6] The prevalence of β-cell autoimmunity in a population is directly related to the incidence of type 1 DM. For example, in Sweden and Finland 3% to 4.5% of the population

have circulating islet cell autoantibodies (ICAs), and this is associated with the highest incidence of type 1 DM in the world: 22 to 35 per 100,000 people. The worldwide prevalence of type 1 DM is increasing, but the cause is not fully understood.[7]

Markers of β-cell autoimmunity can be found in many adults with diabetes.[6] A variant of type 1 DM is called latent autoimmune diabetes of adults (LADA). These patients often have a poor response to oral agents and require insulin therapy much sooner than most patients with type 2 DM. The cause of idiopathic type 1 DM is unknown, but it is not believed to be from an autoimmune process. Idiopathic type 1 DM is most frequently seen in patients of African and Asian descent. These patients have periods of profound hyperglycemia but only intermittently require insulin therapy.

4 Type 2 DM accounts for 90% to 95% of all cases of DM. The prevalence of type 2 DM in the United States is about 12.1% in adults.[2] The risk of developing type 2 DM increases with age and varies widely among racial and ethnic groups.[8] When compared to people of European ancestry, Native Americans, Latino/Hispanic Americans, African Americans, Asian Americans, and Pacific Islanders are more likely to develop type 2 DM. Whether the observed differences in the prevalence of type 2 DM among ethnic and racial groups is primarily due to genetic factors or social factors, such as lifestyle behaviors and cultural behaviors, is unclear. While the prevalence of type 2 DM increases with age, the disorder is increasingly being diagnosed in adolescence and young adulthood. This is likely due to the increasing incidence of obesity and lack of regular physical activity. Genetics plays an important role in the development of type 2 DM. Most cases of type 2 DM appear to be polygenic.

The incidence of GDM is increasing and, between 2007 and 2010, it was estimated to occur in 9% of all pregnancies in the United States.[9] Most women become normoglycemic after pregnancy; however, up to 50% of these women develop type 2 DM later in life.[10]

Other less common (1%-2%) forms of DM occur through a variety of mechanisms.[4] Maturity-onset diabetes of the young (MODY) and neonatal diabetes are inheritable forms of DM caused by specific single-gene mutations. Endocrine disorders, particularly acromegaly and Cushing syndrome, commonly induce hyperglycemia. Diseases that injure or destroy the pancreas such as cystic fibrosis, pancreatitis, and pancreatic cancer can damage β-cells and impair insulin secretion. Several medications can also contribute to hyperglycemia by either impairing insulin secretion, increasing insulin resistance, or both.[5]

ETIOLOGY AND PATHOPHYSIOLOGY

1 DM is caused by derangements in the secretion of insulin, glucagon, and other hormones and results in abnormal carbohydrate and fat metabolism.[6,8] This is often coupled with insulin resistance, particularly in those with type 2 DM. In many cases, the underlying etiology of the disorder is complex and involves multiple mechanisms.

After consuming food, carbohydrate ingestion increases the plasma glucose concentration and stimulates the release of incretin hormones from the gut and insulin release from the pancreatic β-cells.[8] The resultant hyperinsulinemia (1) suppresses hepatic glucose production, (2) suppresses glucagon release, and (3) triggers glucose uptake by peripheral tissues. Upwards of 75% of total body glucose disposal occurs in tissues, including the brain and peripheral nerves, which do not require insulin. Brain glucose uptake occurs at the same rate during fed and fasting periods. The remaining 25% of glucose metabolism takes place in the liver and muscle, tissues that require insulin to promote glucose uptake into the cells. During periods of fasting, approximately 85% of glucose is produced by the liver and the remainder by the kidney.

Although fat tissue is responsible for only a small portion of total body glucose disposal, it plays an important role in glucose homeostasis.[8] Insulin exerts a potent antilipolytic effect, reducing plasma-free fatty acid (FFA) levels. Increased levels of FFAs inhibit the uptake of glucose by muscle and stimulate hepatic gluconeogenesis. Lower FFA concentrations result in increased glucose uptake in muscle and indirectly reduce hepatic glucose production.

Glucagon is produced by pancreatic α cells and is secreted in the fasting state.[8] Glucagon stimulates hepatic glucose production and glycogenolysis. Glucagon and insulin secretion are closely linked. Appropriate secretion of both hormones is needed to keep plasma glucose concentrations within a normal range.

Type 1 Diabetes

Type 1 DM is the result of autoimmune destruction of the β-cells of the pancreas.[6] Given that insulin therapy is required when treating type 1 diabetes,

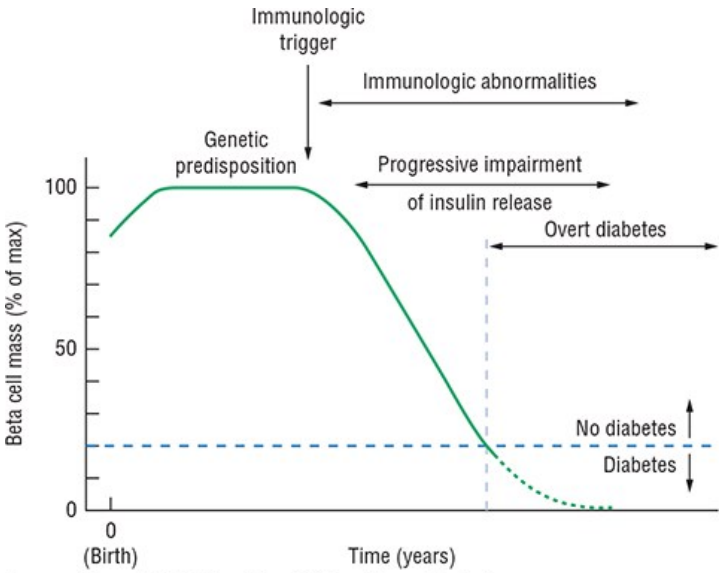
it was previously called insulin-dependent diabetes mellitus, and some references, patients, and providers continue to use this, albeit incorrect, terminology. Type 1 DM is believed to be initiated by exposure to an environmental trigger in a genetically susceptible individual.[11] There is a link between currently known genetic markers for autoimmunity and the development of type 1 DM. However, β-cell autoimmunity develops in less than 10% of the genetically susceptible individuals and progresses to type 1 DM in less than 1%. On the other hand, β-cell autoimmunity, including ICAs, is present at the time of diagnosis in 90% of individuals. Type 1 diabetes most commonly develops in childhood or young adulthood; however, it can occur at any age. Children and adolescents typically have a more rapid rate of β-cell destruction and are more likely to present with DKA. Adults may maintain sufficient insulin secretion to prevent ketoacidosis for many months or years; this slowly progressive form of type 1 DM is sometimes referred to as LADA.

Several genetic polymorphisms have been linked to the development of type 1 DM, including certain human leukocyte antigens (HLA) class II alleles on chromosome 6.[11] Some genetic variants are associated with a higher risk of developing type 1 DM (eg, *DRB1*03-DQB1*0201, DRB1*04-DQB1*302*, and *HLA-B*39*) but others appear to be protective (eg, *DRB1*1501-DQA1*0102-DQB1*0602*). Genetic predisposition to the development of type 1 DM has also been associated with certain polymorphisms in the insulin gene region on chromosome 11. Other genes, including PTPN22, IL2RA, and CTLA-4, may also play a role in some individuals. However, it should be noted that genetic markers are present in only 30% to 50% of patients with type 1 DM. Moreover, only 50% of identical twins and approximately 10% of dizygotic twins develop type 1 DM. Thus, genetic mutations alone do not predict or explain the etiology of the disease.

In order for type 1 DM to develop, a genetically susceptible individual must be exposed to a trigger that initiates the autoimmune process and destruction of pancreatic β-cells.[11] See Fig. 94-1. However, it is unknown precisely what the inciting factors are. Several triggers have been implicated, including early exposure to cow's milk, lack of breastfeeding, gut bacteria (ie, intestinal microbiome), and certain viruses (eg, enterovirus and rotavirus). Although vitamin D deficiency is more prevalent in patients who develop type 1 DM, it is unclear if the relationship is causal or merely an association.

FIGURE 94-1

Clinical course of type 1 diabetes mellitus. *(Adapted from Kaufman ER. Medical Management of Type 1 Diabetes. 6th ed. Alexandria, VA: American Diabetes Association; 2012.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The autoimmune process is mediated by macrophages and T lymphocytes with circulating autoantibodies to various β-cell antigens.[11] The most commonly detected antibody associated with type 1 DM is islet cell autoantibodies (ICAs). Other antibodies may be formed to insulin, glutamic acid decarboxylase 65 (GAD65), insulinoma-associated antigen-2 (IA-2), and zinc transporter 8 (ZnT8). These antibodies are generally considered markers

of disease rather than mediators of β-cell destruction. These markers have been used to identify individuals at risk for type 1 DM and may be useful screening tests to initiate disease prevention strategies. Other autoimmune disorders such as Hashimoto's thyroiditis, Graves' disease, Addison's disease, vitiligo, and celiac sprue are more common in patients with type 1 DM.

In many patients who develop type 1 DM, there is a long preclinical period during which markers of autoimmunity can be detected.[11] β-Cell autoimmunity may precede the diagnosis of type 1 DM by up to 13 years. Autoimmunity remits in some individuals and progresses to absolute β-cell failure in others. Hyperglycemia occurs when 60% to 90% of the β-cells have been destroyed. After the initial diagnosis, there is occasionally a period of transient remission called the "honeymoon" phase during which insulin therapy may not be necessary. Eventually, continued β-cell destruction requires lifelong insulin replacement therapy.

Amylin is a hormone that is co-secreted from the pancreatic β-cell with insulin. Amylin is also deficient in patients with type 1 DM secondary to the destruction of β-cells. Amylin suppresses inappropriate glucagon secretion, slows gastric emptying, and centrally mediated satiety.

Type 2 Diabetes

Type 2 DM is the result of β-cell dysfunction coupled with some degree of insulin resistance.[8] Older references as well as some patients and practitioners continue to call this form of DM noninsulin-dependent diabetes or adult-onset diabetes. Both of these descriptors are erroneous because many patients with type 2 DM will require insulin therapy at some point as β-cell function progressively declines. Moreover, type 2 DM can develop in childhood and is increasingly diagnosed during adolescence. Most individuals with type 2 DM are overweight or obese. Abdominal adiposity is a major contributor to insulin resistance. Genetics play a critical role in the development of type 2 DM as there is a strong inheritance pattern. Hundreds of gene mutations have been linked to the development of type 2 DM. The majority of genetic mutations associated with type 2 DM appear to influence the development and function of β-cells, the sensitivity of cells to insulin action, or the development of obesity. However, none of these single-gene mutations have demonstrated a strong association with type 2 DM. Thus, type 2 DM is likely polygenetic, with more than one genetic defect contributing to its pathogenesis and a diverse combination of derangements contributing to its development in different populations.

In patients with type 2 DM, high blood pressure and dyslipidemia, characterized by high-serum triglycerides and low HDL-cholesterol levels, are very frequent comorbid conditions. Elevated serum plasminogen activator inhibitor-1 (PAI-1), which contributes to a hypercoagulable state, is also common. There are multiple risk factors for the development of type 2 DM.[12] See Table 94-2.

TABLE 94-2

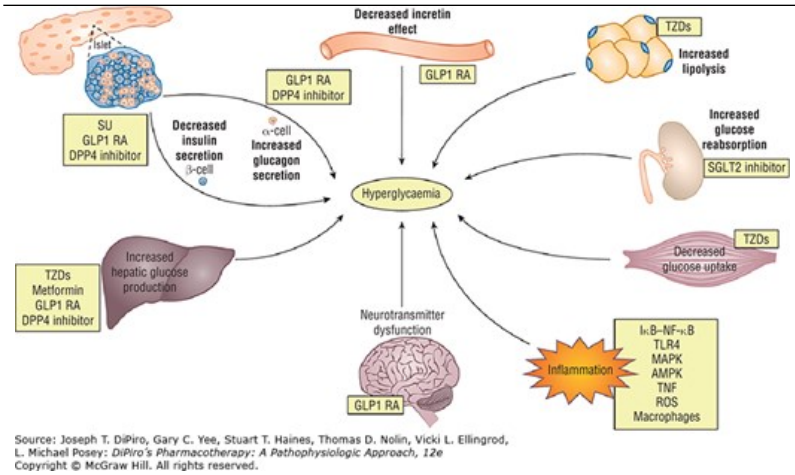
Risk Factors for Type 2 Diabetes

Age ≥45 years old
Overweight or obese (ie, ≥20% over ideal body weight or body mass index [BMI] ≥25 kg/m^2)
First-degree relative with type 2 DM (ie, parent or sibling)
High-risk racial and ethnic groups (ie, African American, Hispanic/Latino, Native American, Asian American, or Pacific Islander)
Sedentary lifestyle (ie, limited daily physical activity)
History of impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or elevated A1C ≥5.7%
Hypertension (≥130/90 mm Hg in adults or on therapy for hypertension)
Dyslipidemia (high-density lipoprotein [HDL] cholesterol ≤35 mg/dL (0.91 mmol/L) or a triglyceride level ≥250 mg/dL (2.83 mmol/L)
History of GDM or delivery of a baby weighing more than 9 lb (4 kg)
History of vascular disease (eg, myocardial infarction, ischemic stroke, peripheral arterial disease)
Presence of acanthosis nigricans (ie, dark, thick, and velvety skins around the neck or armpits)
Polycystic ovary syndrome

Most patients who develop type 2 DM have multiple defects that impact the regulation of plasma glucose: (1) impaired insulin secretion; (2) deficiency and resistance to incretin hormones; (3) insulin resistance involving muscle, liver, and adipocytes; (4) excess glucagon secretion; (5) increased hepatic glucose production; (6) upregulation of the sodium-glucose cotransporter in the kidney; (7) systemic inflammation; and (8) diminished satiety.[8] See Fig. 94-2.

FIGURE 94-2

Pathophysiology of type 2 diabetes mellitus. Multiple defects known as the ominous octet. *(Reproduced, with permission, from Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773-95.)*

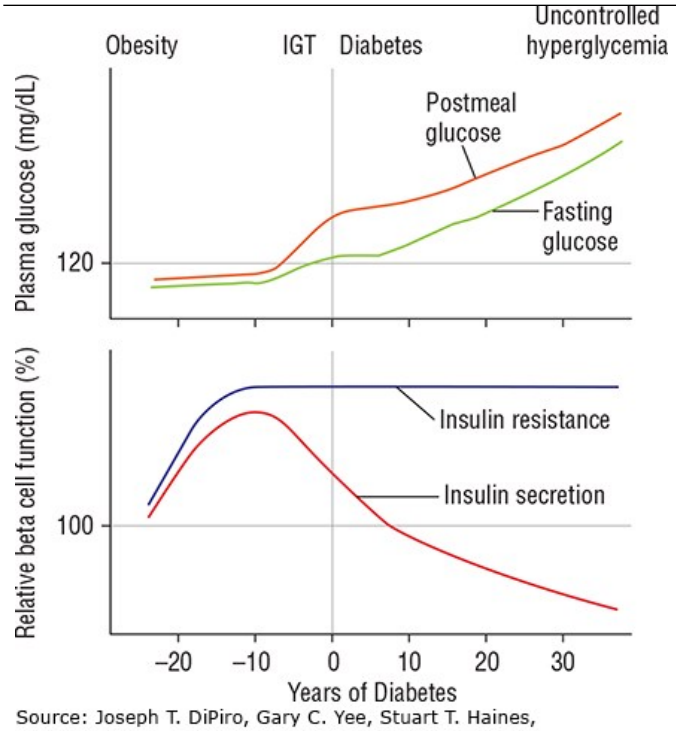


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

The pancreas in people with normal-functioning β-cells is able to adjust insulin secretion to maintain normal plasma glucose levels. In obese individuals who do not yet have diabetes, insulin increases in proportion to the severity of the insulin resistance, and plasma glucose remains normal. Impaired insulin secretion is therefore requisite for the development of type 2 DM. In the early stages of β-cell dysfunction, first-phase insulin release is deficient, resulting in impaired glucose tolerance (IGT) (Fig. 94-3). First-phase insulin involves the release of stored insulin in the β-cell and acts to "prime" the liver for nutrient intake. Without appropriate first-phase insulin release, second-phase insulin must compensate for the subsequent postprandial carbohydrate load in order to normalize glucose levels. When insulin release is no longer sufficient to normalize plasma glucose, dysglycemia, including prediabetes and diabetes, ensue. In patients with type 2 DM, β-cell mass and function are both reduced. β-Cell failure is progressive, starting years prior to the diagnosis of diabetes. People with type 2 DM lose approximately 5% to 7% of β-cell function per year. Progressive β-cell loss is likely the result of several factors, including (1) glucotoxicity; (2) lipotoxicity; (3) insulin resistance; (4) age; (5) genetics; and (6) incretin deficiency. Glucotoxicity occurs when glucose levels chronically exceed 140 mg/dL (7.8 mmol/L). The β-cell is unable to maintain sufficient insulin secretion and, paradoxically, releases less insulin as glucose levels increase.

FIGURE 94-3

Natural history of type 2 diabetes. (IGT, impaired glucose tolerance.) For several years prior to the onset of overt hyperglycemia, β-cell dysfunction and the progressive loss of β-cells begins. Moreover, resistance to the action of insulin in muscle and fat tissue is accelerated by weight gain and central adiposity. With increasing insulin resistance and β-cell dysfunction, post-prandial blood glucose concentrations become abnormal. However, fasting blood glucose concentrations typically remain normal or only slightly elevated. As β-cell loss continues, fasting blood glucose readings begin to rise. It is at this point that most patients are diagnosed. Initial treatments improve glycemic control by improving insulin secretion or reducing insulin resistance, or both. Over time, as β-cell loss continues and insulin secretion dwindles to <20% of normal, near-normal blood glucose concentrations cannot be achieved without supplemental insulin therapy. Blood glucose values in mg/dL can be expressed in mmol/L by multiplying by 0.0555.



Gestational Diabetes

GDM develops during pregnancy.[13] If DM is diagnosed prior to pregnancy, this is not GDM, but rather pregnancy with preexisting DM. Hormone changes during pregnancy result in increased insulin resistance, and GDM may ensue if the mother cannot increase insulin secretion to adequately compensate to maintain normoglycemia. Women who develop GDM are predisposed to subsequently developing type 2 DM. GDM and type 2 DM likely share much of the same etiological causes. In most cases, glucose intolerance first appears near the beginning of the third trimester. However, risk assessment and intervention should begin from the first prenatal visit. Detection is important, as therapy will reduce perinatal morbidity and mortality.

Other Types of Diabetes

MODY is characterized by impaired insulin secretion in response to a glucose stimulus with minimal or no insulin resistance.[4] Patients typically exhibit mild hyperglycemia at an early age, and diagnosis is often delayed. The disease is inherited in an autosomal-dominant pattern with at least six different mutations identified to date. MODY 2 and 3 are most common.

The production of mutant insulin molecules has been identified in a few families and also results in abnormal glucose intolerance. Several genetic mutations have been described in the insulin receptor and are associated with insulin resistance. Type A insulin resistance is a clinical syndrome characterized by acanthosis nigricans, virilization in women, polycystic ovaries, and hyperinsulinemia. Anti-insulin receptor antibodies may block the binding of insulin. This has been referred to as type B insulin resistance.

CLINICAL PRESENTATION

Characteristic	Type 1 DM	Type 2 DM
Typical age at diagnosis	<20 years[a]	>30 years[b]
Body habitus	Lean (BMI <25 kg/m^2)	Overweight or obese (BMI ≥25 kg/m^2); abdominal obesity and increased waist:hip ratio
Family history of DM in first-degree relatives	Uncommon (<10%)	Common (>80%)
Insulin resistance	Uncommon (occurs if obese)	Very common
Autoantibodies	Usually present	Rarely present
Onset	Abrupt (days/weeks)	Gradual (years)
Symptoms[c]	Common and may be dramatic	Uncommon and often mild
Ketosis	Prone	Rare
Acute complication	Diabetic ketoacidosis (DKA)	Hyperosmolar hyperglycemic state (HHS)
Need for insulin replacement therapy	Immediate	Years after diagnosis
Long-term complications present at diagnosis	Rare—screening for complications unnecessary	Common—screening for complications recommended

[a]While most patients are diagnosed before age 20, type 1 DM can occur at any age.

[b]While most patients are diagnosed after age 30, type 2 DM is increasingly common in obese adolescents and young adults, especially in high-risk populations (eg, Black Americans, Latino/Hispanic Americans, Native Americans).

[c]The classic symptoms of DM include polyuria, polydipsia, polyphagia, weight loss, and fatigue.

The clinical presentation and features of type 1 DM and type 2 DM are different. Although type 1 DM can develop at any age, most patients are diagnosed before the age of 20. Patients with type 1 DM are often lean or thin at the time of diagnosis. In the absence of an adequate supply of insulin, patients with type 1 DM are prone to developing ketoacidosis and many initially present with DKA. Patients with type 1 DM often have symptoms in the days or weeks preceding the diagnosis. These symptoms often include frequent urination (polyuria) due to an osmotic diuresis from glucosuria, excessive thirst (polydipsia) due to dehydration, increased appetite (polyphagia), and weight loss due to caloric loss. Fatigue and lethargy are also common. The onset of symptoms can be triggered by an infection, trauma, or psychological stress.

In contrast, a majority of patients with type 2 DM are asymptomatic or have only mild fatigue at the time of diagnosis. Many patients are incidentally discovered to have type 2 DM based on the results of a routine laboratory test (eg, plasma glucose or A1C) or development of complications (eg, myocardial infarction, stroke, kidney impairment). Mild hyperglycemia is likely present for many years prior to the diagnosis and thus explains why both microvascular and macrovascular complications are often present at the time of diagnosis. Most patients with type 2 DM are overweight or obese with an elevated waist:hip ratio. Many will report having first-degree relatives with diabetes.

Diagnosis of Diabetes

The diagnosis of diabetes requires the use of glycemic cut points that discriminate patients with normal BG from patients with IFG, IGT, and diabetes (Tables 94-4 and 94-5). The cut points are meant to reflect the level of glucose above which microvascular complications have been shown to increase.[4] Cross-sectional studies have shown a consistent increase in the risk of developing retinopathy at an FPG level above 116 mg/dL (6.4 mmol/L), a 2-hour PPG level above 185 mg/dL (10.3 mmol/L), and an A1C above 6.0% (0.060; 41-42 mmol/mol).

TABLE 94-3

Definitions of Normal and Abnormal Glycemia

Fasting plasma glucose (FPG)	
Normal fasting glucose	70-99 mg/dL (3.9-5.5 mmol/L)
Impaired fasting glucose (IFG)	100-125 mg/dL (5.6-6.9 mmol/L)
Diabetes mellitus	≥126 mg/dL (7.0 mmol/L)
2-hour post-load plasma glucose (oral glucose tolerance test)	
Normal glucose tolerance	<140 mg/dL (7.8 mmol/L)
Impaired glucose tolerance (IGT)	140-199 mg/dL (7.8-11.0 mmol/L)
Diabetes mellitus	≥200 mg/dL (11.1 mmol/L)
Glycosylated hemoglobin (A1C)	
Normal A1C	4-5.6% (0.04-0.056; 20-38 mmol/mol)
Increased risk of diabetes mellitus (Prediabetes)	5.7-6.4% (0.057-0.064; 39-46 mmol/mol)
Diabetes mellitus	≥6.5% (0.065; 48 mmol/mol)

Data from Reference 4.

If an NGSP (previously known as the National Glycohemoglobin Standardization Program) method is used, the A1C is the logical test for the diagnosis of diabetes as it measures glycemic exposure over the last 2 to 3 months, in contrast to a single-day, single-point glucose measurement. In addition, patients do not need to fast, and the A1C is a readily available test. An A1C of 6.0% to 6.4% (0.06-0.064; 42-46 mmol/mol) denotes a 10-fold increase in the risk of developing diabetes but does not consistently identify patients with impaired fasting glucose or impaired glucose tolerance. There are slight racial differences in normal A1C levels. One-third fewer individuals with diabetes are identified using the A1C ≥6.5% (0.065; 48 mmol/mol) threshold versus an FPG ≥126 mg/dL (7.0 mmol/L), yet providers may be more likely to diagnose diabetes from an A1C than from an elevated FPG level. While an A1C ≥6.5% (0.065; 48 mmol/mol) is perhaps the most convenient and sensitive method of diagnosing DM, there are three other criteria that can be used to diagnose DM in nonpregnant adults. See Table 94-4. If the patient has symptomatic hyperglycemia and a random plasma glucose ≥200 mg/dL (11.1 mmol/L), reconfirming the diagnosis is not required.

TABLE 94-4

Criteria for the Diagnosis of Diabetes Mellitus

1. A1C ≥6.5% (0.065; 48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.[a]
2. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.[a]
3. Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.[a]
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose concentration ≥200 mg/dL (11.1 mmol/L).

[a]In the absence of unequivocal hyperglycemia, a diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Data from Reference 4.

Serial measurements at clinician-defined intervals can help to identify patients moving toward diabetes and those who are stable. Patients who have even minor increases in glucose or A1C values over time should be followed more closely as they are more likely to progress to DM. The A1C measurement can be affected by anemias and several hemoglobinopathies, which would necessitate the use of one of the plasma glucose criteria in these individuals. More information about the A1C assay can be found at the NGSP website: http://www.ngsp.org/interf.asp.

Screening for Diabetes

Given the long-term complications associated with DM and the positive impact that early interventions can have on hyperglycemia and health outcomes, efforts to screen at-risk patients for impaired FPG and the development of diabetes are recommended. Screening begins with identifying patients who are at risk for developing diabetes and, once identified, encouraging patients to obtain an FPG and A1C measurement.

Type 1 Diabetes

The prevalence of type 1 DM is low in the general population. Due to the acute onset of symptoms in most individuals, screening for type 1 DM in asymptomatic children or adults is not recommended.[4] Screening for β-cell autoantibody status in high-risk family members may be appropriate in the context of clinical research trials for the prevention of type 1 DM.

Type 2 Diabetes

The ADA recommends screening for type 2 DM in adults who are overweight (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian-Americans) and have at least one other risk factor for the development of type 2 DM.[4] See Table 94-2. The risk of type 2 DM increases with age, and therefore all adults, even those without risk factors, should be screened every 3 years starting at 35 years old. The recommended screening tests are an A1C and FPG or 2-hour oral glucose tolerance test (OGTT). The optimal time between screening tests is not known, but it may be prudent to screen patients with multiple risk factors every year.

Children and Adolescents

Despite a lack of clinical evidence to support widespread testing of children for type 2 DM, it is clear that more children and adolescents are developing type 2 DM. The ADA recommends screening overweight (defined as BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal) youths who have at least one of the following risk factors: a family history of type 2 DM in first- and second-degree relatives; Native Americans, African Americans, Latinos, Asian Americans, andPacific Islanders; those with signs or conditions associated with insulin resistance (eg, acanthosis nigricans, hypertension, dyslipidemia); or maternal history of diabetes or GDM during the child's gestation.[4] Screening should be done every 3 years starting at age 10 years or at the onset of puberty if it occurs at a younger age.

Gestational Diabetes

Risk assessment for GDM should occur at the first prenatal visit. Due to the high prevalence of obesity and undiagnosed DM, women with multiple risk factors for type 2 DM should be tested as soon as feasible.[4] All women, even if the initial screen test at the first prenatal visit was negative, should undergo testing between weeks 24 and 28 of gestation. Screening for GDM may be done in one of two ways: (1) a one-step strategy using a fasting 75-g OGTT, or (2) a two-step strategy starting with a nonfasting 50-g glucose load test (GLT). With the standard 75-g OGTT, the diagnosis of GDM is confirmed when fasting, 1-hour, 2-hour, and/or 3-hour glucose values are equal or greater to cut-off values. If a nonfasting 50-g GLT is performed, a fasting 100-g glucose tolerance test must be performed if the 1-hour value is elevated. See Table 94-5.

TABLE 94-5

Screening for and Diagnosis of Gestational Diabetes Mellitus (GDM)

1. One-step method (fasting 75-g OGTT)[a]	
One abnormal value is diagnostic of GDM	
Time	**Plasma Glucose**
Fasting	≥92 mg/dL (5.1 mmol/L)
1 hour	≥180 mg/dL (10.0 mmol/L)
2 hours	≥153 mg/dL (8.5 mmol/L)
2. Two-step method	
Step 1: Perform a 50-g OGTT (nonfasting) at 24-28 weeks of gestation in women not previously diagnosed with diabetes	
1 hour	≥140 mg/dL[b] (7.8 mmol/L)
Step 2: If a screening test is positive, perform 100-g OGTT (fasting)	
Two or more abnormal values are diagnostic for GDM	
Fasting	95 mg/dL (5.3 mmol/L)
1 hour	180 mg/dL (10.0 mmol/L)
2 hours	155 mg/dL (8.6 mmol/L)
3 hours	140 mg/dL (7.8 mmol/L)

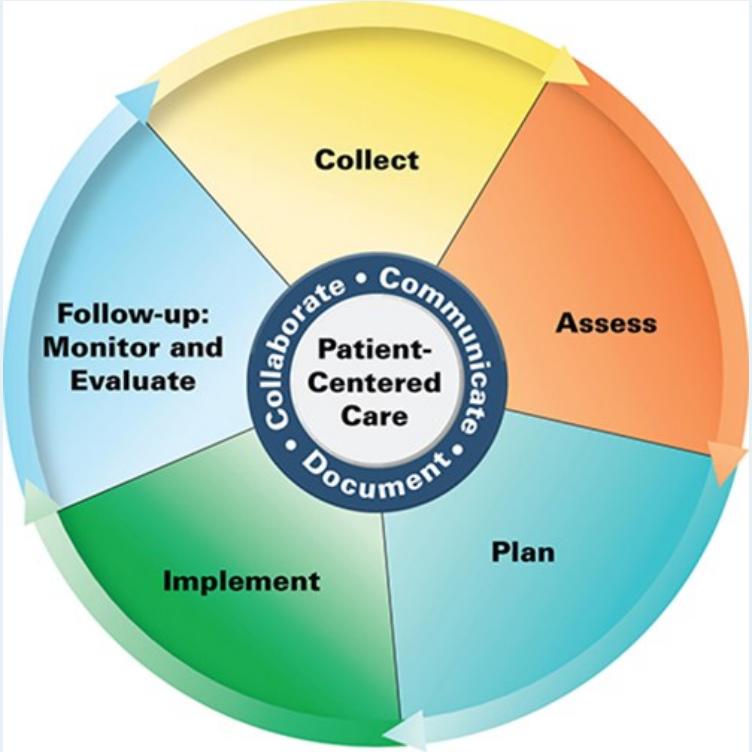
[a]Should be performed at 24-28 weeks gestation unless the patient has diabetes. The test should be done in the morning after an 8- to 14-hour fast.

[b]The ACOG recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic populations with a higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

Data from Reference 4.

PATIENT CARE PROCESS

Patient Care Process for the Management of Diabetes Mellitus



Collect

- Patient characteristics (eg, age, sex, reproductive status)
- Characteristics of diabetes (eg, type, age of onset, initial presentation)
- Microvascular and macrovascular complications
- Hypoglycemia episodes, symptoms, frequency, and suspected cause(s)
- History of diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome (HHS)—frequency, severity, and suspected cause(s)
- Patient history (past medical, family, social—dietary habits, weight history, sleep behaviors, physical activity)
- Current medications (including complementary and alternative therapies) and medication-taking behaviors (eg, adherence, injection technique)
- Past diabetes treatments, response to therapy, the reason for discontinuation
- Diabetes and nutritional education (currently enrolled and completed)
- Self-monitoring of blood glucose (BGM) or continuous glucose monitoring (CGM) results and self-management behaviors
- Social and cultural issues—preferences, values, and beliefs; health literacy; insurance coverage and ability to afford treatments
- Physical exam: height, weight, BMI, blood pressure, heart rate, comprehensive foot exam

- Labs (eg, glucose, hemoglobin A1c [A1C], serum creatinine [Scr], blood urea nitrogen [BUN], estimated glomerular filtration rate [eGFR], fasting lipid panel [FLP], urine albumin to creatinine ratio [UACR], serum electrolytes)

Assess

- Diagnosis and classification (see Tables 94-1, 94-3, and 94-4)
- Microvascular and macrovascular complications and potential comorbid conditions
- Achievement of A1C and glycemic goals (see Table 94-6)
- Appropriateness, effectiveness, safety/tolerability, treatment burden, cost, and adherence to the current antihyperglycemic regimen
- Achievement of weight, lifestyle, and other behavioral goals
- Achievement of goals for comorbidities (eg, blood pressure, lipids, neuropathic pain)
- Screen for depression, anxiety, disordered eating
- Assess psychosocial factors, social determinants of health, and other barriers to diabetes self-management and treatment

Plan*

- Appropriate A1C and glycemic goals based on age, comorbidities, and other factors (see Table 94-6)
- Tailored lifestyle modifications (eg, diet, exercise, weight management)
- Drug therapy regimen including specific antihyperglycemic agent(s), dose, route, frequency, and duration; specify continuation and discontinuation of existing therapies (see Tables 94-7 to 94-11)
- Monitoring parameters including efficacy (eg, A1C, BGM) safety (medication-specific adverse effects, hypoglycemia), and timeframe (see Table 94-11)
- Patient education (eg, the purpose of treatment, drug administration, dietary and lifestyle modification)
- Referrals to other providers when appropriate (eg, diabetes care and education specialist, registered dietician, eye care professional, podiatrist, social worker, mental health professional)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up including telehealth visits to monitor and adjust treatment

Follow-Up: Monitor and Evaluate

- Determine A1C and glycemic goal attainment
- Identify the presence of medication-related adverse effects (see Table 94-10)
- Assess occurrence/development/progression of diabetes-related complications
- Evaluate patient adherence to treatment plan using multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

General Approach to Treatment

During an initial visit, a thorough medical evaluation should be completed to confirm the diagnosis, classify the type of diabetes, evaluate for any complications or potential comorbid conditions, and review previous treatments and risk factors. Past medical, family, and social history should be collected as well as medication use history including adherence, tolerability, and use of diabetes technology. An assessment of lifestyle behaviors, psychosocial factors, and social determinants of health, self-management education needs, and hypoglycemia should occur. A thorough physical exam (including height, weight, BMI, blood pressure, thyroid palpitation, and foot exam) and laboratory evaluation (including A1C, lipid profile, liver function tests, serum creatinine,eGFR, and UACR) should be performed. A 10-year atherosclerotic cardiovascular disease (ASCVD) risk score should also be calculated.[14,15]

Goals of Therapy

6 7 The primary goals of therapy for DM are to prevent or delay the progression of long-term micro- and macrovascular complications including retinopathy, neuropathy, diabetic kidney disease, and ASCVD. Additional goals of therapy are to alleviate symptoms of hyperglycemia, minimize hypoglycemia and other adverse effects, minimize treatment burden, and maintain quality of life. This requires glycemic control as well as control of comorbidities and CV risk factors. Glycemic control has well-documented benefits in terms of reducing both short-term and long-term complications associated with DM, but overly intensive control has also led to poor outcomes. Thus, glycemic targets should be individualized for each patient and should be based on balanced considerations of clinical trial evidence,patient-specific factors, and cost.[15,16]

Evidence to Support Intensive Glycemic Control

The first trial to definitively prove that good glycemic control could prevent or delay diabetes-related complications was the Diabetes Complications and Control Trial (DCCT).[17] The DCCT enrolled patients with type 1 DM. Patients in the intensive group were treated with intensive basal-bolus insulin therapy (three or more insulin injections per day or insulin pump), with frequent alterations of insulin therapy based on blood glucose monitoring (BGM) results plus frequent contact with a health professional. Patients in the conventional therapy were treated with one or two insulin injections per day. After 6.5 years, retinopathy, neuropathy, and nephropathy were significantly reduced in the intensive group, but symptomatic and severe hypoglycemia was significantly more frequent. Long-term follow-up of the trial participants demonstrated a reduction in macrovascular complications as well as persistent reductions in microvascular complications, even though the difference in A1C values between treatment groups disappeared over time.[18,19]

Another landmark clinical trial, The United Kingdom Prospective Diabetes Study (UKPDS), enrolled more than 5,000 patients with type 2 DM between 1977 and 1991. Patients were followed for an average of 10 years to determine the impact of intensive versus conventional glycemic control on the incidence of long-term complications in patients with newly diagnosed type 2 DM. The results showed that intensive glycemic control (using sulfonylureas and insulin) achieved an A1C of 7.0% (0.070; 53 mmol/mol) compared to 7.9% (63 mmol/mol) in the conventional group. This translated into a modest but significant (12%) reduction in diabetes-related complications, most of which was due to a 25% reduction in microvascular complications.[20] Intensive glucose control using metformin as the initial therapy lowered the risk of diabetes-related complications by 32%, diabetes-related death by 42%, and all-cause mortality by 36% compared to conventional treatment in an overweight cohort of patients.[21] In the long-term UKPDS follow-up study, microvascular benefits of good glycemic control persisted 10 years after the end of the original trial, and a significant long-term reduction in myocardial infarction (MI) and all-cause mortality emerged in the intensive glucose control arm.[22]

Three additional large clinical trials were performed after the UKPDS to compare the effects of different intensities of glycemic control on the risk of macrovascular complications. These studies were done in patients with long-standing type 2 DM who were at high risk for ASCVD. The Action to Control CV Risk in Diabetes (ACCORD) study showed that lower A1C levels (achieved mean A1C 6.4% vs 7.5% [0.064 vs 0.075; 46 vs 58 mmol/mol]) reduced the risk of some microvascular complications but did not reduce the risk of macrovascular complications. The risk of hypoglycemia was significantly higher in the intensive treatment group. Most importantly, this study was stopped early due to an increase in mortality in the intensive treatment arm.[23] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study similarly showed no

significant differences in ASCVD outcomes between two levels of glycemic control (achieved mean A1C 6.3% vs 7.0% [0.063 vs 0.070; 45 vs 53 mmol/mol]) but did show that the more intensive glucose control reduced microvascular complications.[24] The Veterans Affairs Diabetes Trial (VADT) also suggested reduced microvascular complications but no significant reduction in ASCVD outcomes with more intensive glycemic control (6.9% vs 8.5% [0.069 vs 0.085; 52 vs 69 mmol/mol).[25] Based on the results of these studies, there appear to be some benefits in terms of microvascular complications but not ASCVD outcomes from intensive glycemic control. However, achieving more stringent glucose targets requires more intensive treatment, which is often more complex and costly, and increases the risk of severe hypoglycemia when insulin therapy is used. The short-term and long-term benefits and risks must be carefully considered when setting intensive glycemic targets.

Glycemic Targets

Based on the clinical evidence that glycemic control reduces microvascular complications and also has long-term benefits in reducing macrovascular complications, several organizations, including the ADA and AACE, recommend surrogate targets for glycemic control. The ADA Standards of Care indicate that an A1C <7% (0.07; 53 mmol/mol) is reasonable for most nonpregnant adults. A fasting or preprandial plasma glucose (FPG) target range of 80 to 130 mg/dL (4.4 and 7.2 mmol/L) and a peak postprandial plasma glucose (PPG) target of <180 mg/dL (10.0 mmol/L) (1-2 hours after the beginning of a meal) correspond with an A1C target <7% (0.07; 53 mmol/mol).[16] If using an ambulatory glucose profile (AGP) or a glucose management indicator (GMI) from a continuous glucose monitor (CGM) to assess glycemia, a parallel goal is time in range (TIR) of >70% with time below range (TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% TIR with <1% TBR is recommended. The AACE guidelines are more aggressive and indicate that an A1C ≤6.5% (0.065; 48 mmol/mol) is optimal if it can be achieved in a safe and affordable manner. An FPG target of <110 mg/dL (6.1 mmol/L) and a 2-hour PPG target of <140 mg/dL (7.8 mmol/L) correspond with this recommendation (Table 94-6).[26]

TABLE 94-6

Glycemic Target Recommendations in Various Populations

Glycemic targets for most nonpregnant adults with diabetes[a]		
	American Diabetes Association	**American Association of Clinical Endocrinologists**
Glycosylated hemoglobin (A1C)	<7.0% (0.07; 53 mmol/mol)	≤6.5 (0.065; 48 mmol/mol)
Fasting/preprandial plasma glucose (FPG)	80-130 mg/dL (4.4-7.2 mmol/L)	<110 mg/dL (6.1 mmol/L)
Peak postprandial glucose (PPG)	<180 mg/dL (10.0 mmol/L)	<140 mg/dL (7.8 mmol/L)
Time in range (TIR); % of CGM readings and time between 70 and 180 mg/dL (3.9-10.0 mmol/L)	>70%	
Time below range (TBR); % of CGM readings and time <70 mg/dL (3.9 mmol/L)	<4%	
Glycemic variability (% CV)	<36%	
Glycemic targets for adolescents and children		
A1C	<7.0% (0.07; 53 mmol/mol)	
FPG/preprandial glucose	90-130 mg/dL (5.0-7.2 mmol/L)	
Bedtime or overnight glucose	90-150 mg/dL (5.0-8.3 mmol/L)	

Glycemic targets for pregnant women			
A1C	<6.5% (0.065; 48 mmol/mol)		
FPG or premeal glucose	<95 mg/dL (5.3 mmol/L)		
Postprandial glucose (1 hr)	<140 mg/dL (7.8 mmol/L)		
Postprandial glucose (2 hr)	<120 mg/dL (6.7 mmol/L)		
American Diabetes Association glycemic targets for older adults			
Patient characteristics/health status	A1C	FPG or preprandial glucose	Bedtime glucose
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	<7.0%-7.5% (0.07-0.075; 53-58 mmol/mol)	80-130 mg/dL (4.4-7.2 mmol/L)	80-180 mg/dL (4.4-10 mmol/L)
Complex/intermediate (multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)	<8.0% (0.080; 64 mmol/mol)	90-150 mg/dL (5.0-8.3 mmol/L)	100-180 mg/dL (5.6-10.0 mmol/L)
Very complex/poor health (LTC or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2+ ADL dependencies)	Avoid reliance on A1C; avoid hypoglycemia and symptomatic hyperglycemia	100-180 mg/dL (5.6-10.0 mmol/L)	110-200 mg/dL (6.1-11.1 mmol/L)

ADL, activities of daily living; CGM, continuous glucose monitoring; CV, coefficient of variation; LTC, long-term care

[a]Glycemic targets should be individualized. More or less stringent goals may be appropriate for some patients.

Many patients now use a CGM device to assist with glucose management. The use of a CGM can be beneficial for many patients with diabetes and is recommended in patients who use intensive insulin therapy and for those who experience severe or frequent hypoglycemia. A CGM device can report the percentage of time in, above, and below the recommended target ranges and can report the variability of glucose readings. Ideally, the time in range, defined as 70 to 180 mg/dL (3.9 to 10.0 mmol/L), should be at least 70% and the time below range, defined as <70 mg/dL (3.9 mmol/L), should be less than 4%. A CGM device can also report glucose variability, an outcome that is increasingly being recognized as a clinically meaningful outcome beyond A1C. Emerging data indicates that, regardless of A1C, fluctuations in glucose are associated with increased risk of diabetes complications, and A1C alone does not provide the full picture of glycemic control (see Fig. 94-4). Glucose variability is defined as the percent coefficient of variation (%CV) and should be ≤36%.[16] These glucose statistics can be viewed through the ambulatory glucose profile (AGP) report, which also includes a summary glucose profile graph and daily glucose graphs (see Fig. 94-5). The AGP report is a standardized, single-page report that is easy to interpret and provides consistent data regardless of what device is being used.[27]

FIGURE 94-4

Glucose variability.

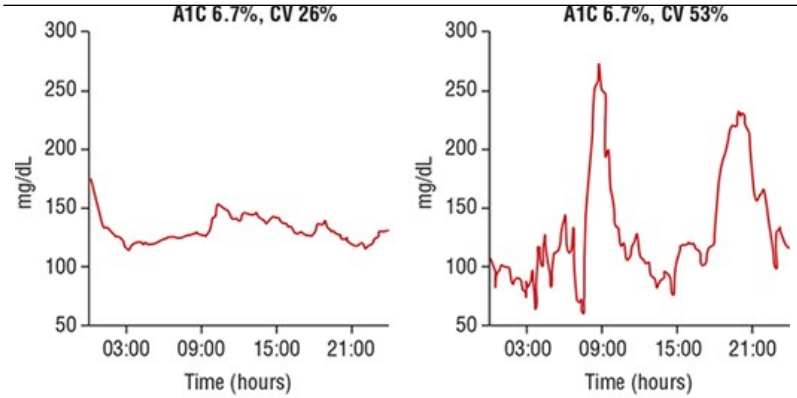
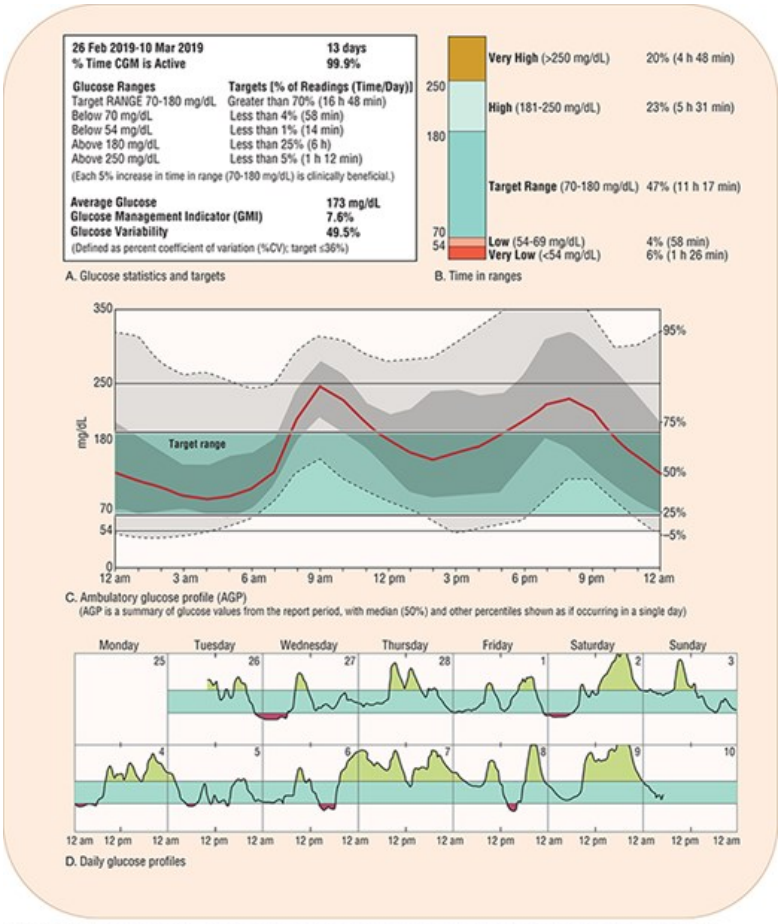


FIGURE 94-5

Ambulatory glucose profile report from a continuous glucose monitoring device.

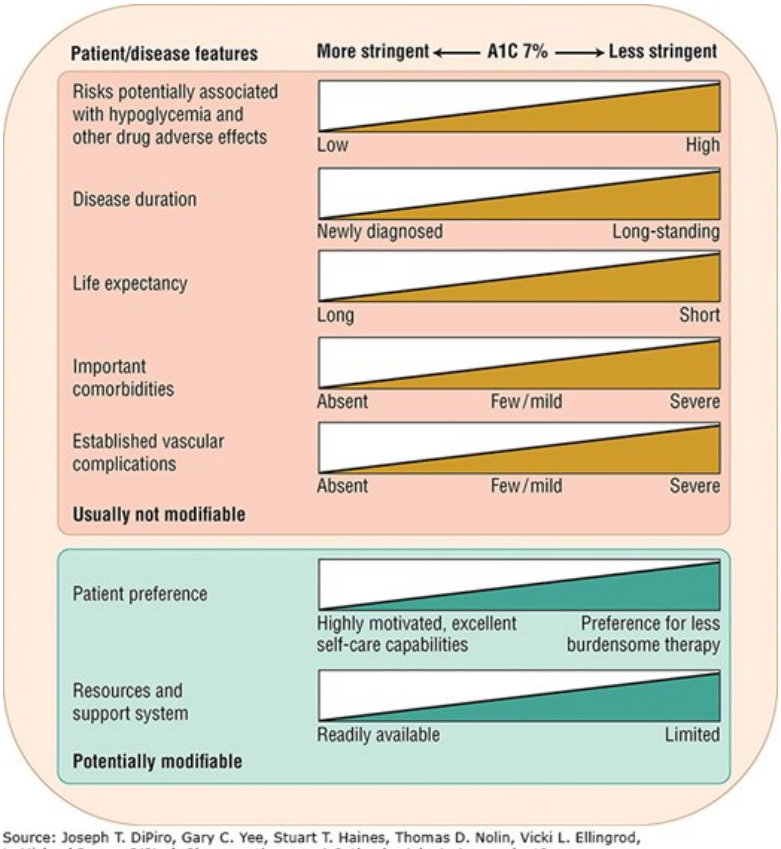


Glycemic targets must be individualized based on patient-specific factors and the potential risks and benefits of treatment (see Fig. 94-6). Ideally, glycemic targets should be established at the time of diagnosis and then reviewed and re-evaluated at each visit. When possible, these decisions should be made in collaboration with the patient. Patient or disease factors to consider include treatment-related risks including hypoglycemia and other adverse effects, ability to sense or articulate hypoglycemia symptoms, disease duration, life expectancy, comorbidities, established vascular complications, patient attitude and expected treatment effort, access to CGM or other resources, and support system. While an A1C <7% (0.07; 53

mmol/mol) is recommended for most patients, a more stringent goal (such as <6.5% [0.065; 48 mmol/mol]) may be appropriate for some patients if it can be achieved without significant adverse effects, particularly hypoglycemia. Those patients might be younger, with a long life expectancy, with a short duration of diabetes, those treated only with lifestyle modifications and medications unlikely to cause hypoglycemia, or those without significant comorbidities. Less stringent goals (such as <8% [0.08; 64 mmol/mol]) may be appropriate for patients who are older or who have a long duration of diabetes, a history of severe hypoglycemia, numerous comorbidities, or advanced complications. A higher A1C goal may also be appropriate for a patient in whom it remains difficult to achieve the goal despite appropriate education, monitoring, and drug therapy. For those treated with complex medication regimens, especially those that include insulin, the risk of trying to achieve stringent glycemic goals may outweigh the benefit.

FIGURE 94-6

Approach to individualizing glycemic targets. *(Adapted from American Diabetes Association.)* Higher A1C goals should be considered in adolescents and children as well as patients older than 65 years (Table 94-6).[28] An A1C goal <7.5% (0.075; 58 mmol/mol) is reasonable for healthy older adults, while an A1C goal <8.0% (0.080; 64 mmol/mol) should be considered for those with coexisting chronic diseases, impairments of activities of daily living, cognitive impairment, or who reside in long-term care facilities. In older adults with limited life expectancy, multiple comorbid conditions, or limited cognition, the A1C should not be used to guide therapy.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

NONPHARMACOLOGIC THERAPY

8 Nonpharmacologic therapy such as medical nutrition therapy (MNT), physical activity, glucose monitoring, and diabetes self-management education (DSME) is a cornerstone of treatment for all patients with diabetes.

Medical Nutrition Therapy

MNT is an evidence-based medical approach to treating diabetes through the use of an individually tailored nutrition plan. There is no standardized

"diabetes diet," nor is there a single ideal distribution of macronutrients; therefore, meal planning should be individualized. It is imperative that patients understand the interrelationships between carbohydrate intake, medications, weight, and glucose control. A healthy meal plan that is moderate in calories and carbohydrates and low in saturated fat, with all of the essential vitamins and minerals, is recommended. A Mediterranean-style diet rich in mono- and polyunsaturated fats may have glucose and CV benefits and could be considered.[29]

Weight loss or weight maintenance is a crucial element in many patients with type 2 DM. An initial weight loss goal of at least 5% should be targeted in all patients who are overweight or obese through calorie restriction. Strategies to reduce calories include reducing portions and frequency of food intake, decreasing the consumption of empty calories, added sugars, and saturated fats, increasing nutrient-dense foods (eg, nonstarchy vegetables), employing low-calorie cooking methods, and tracking calorie intake. Helping the patient adopt healthier eating behaviors that lead to sustained weight loss over time is more important than a specific diet.[29]

Carbohydrate counting is another valuable component of diabetes care. The appropriate amount (grams) and type of carbohydrates are controversial. For individuals with type 1 DM, the focus is more on physiologically regulating insulin administration. For those on fixed doses of mealtime insulin, consistent intake of carbohydrates is recommended to improve glucose control and minimize hypoglycemia. For those on flexible insulin dosing regimens (eg, matching insulin doses to carbohydrate intake amounts), accurate carbohydrate counting to determine mealtime insulin doses is required. For patients with type 2 DM, carbohydrate counting focuses more on a balanced diet with moderate carbohydrate intake at each meal to minimize glucose excursions. Carbohydrate intake from vegetables, fruits, legumes, whole grains, dairy products, and those high in fiber is preferred. Sugar-sweetened beverages and foods with added sugars should be discouraged. Financial constraints and cultural food practices must also be considered. Discourage bedtime and between-meal snacks, set realistic goals, determine what the patient is willing to change, and follow up to see how and whether those changes were implemented.[29]

Physical Activity

Most patients with diabetes benefit from regular physical activity. Aerobic exercise improves insulin sensitivity, modestly improves glycemic control in the majority of individuals, reduces CV risk, contributes to weight loss or maintenance, and improves well-being. Patients should choose activities that they enjoy and are likely to do at regular intervals. Start exercise slowly in previously sedentary patients. It is unclear if asymptomatic patients should be screened for ASCVD prior to beginning an exercise regimen. Screening is reasonable in patients with long-standing disease (more than or equal to 10 years), multiple CV risk factors, microvascular disease (especially kidney disease), or evidence of atherosclerotic disease. If the patient has uncontrolled hypertension, autonomic neuropathy, insensate feet, or proliferative retinopathy, restrictions on recommended activities are recommended. Physical activity goals include at least 150 minutes per week of moderate (50%-70% maximal heart rate) intensity exercise spread over at least 3 days a week with no more than 2 days between activities. In addition, resistance/strength training is recommended at least two times a week as long as the patient does not have proliferative diabetic retinopathy.[29]

Glucose Monitoring

Patients with diabetes should be reassessed every 3 to 6 months (3 months if uncontrolled and 6 months if controlled). An A1C should be drawn, and treatment should be adjusted as needed.[16]

Patients on intensive insulin therapy should BGM at least four times daily, before meals and at bedtime, or should use a CGM device. Patients should also test before exercise, prior to critical tasks such as driving, and if symptoms of hypoglycemia occur. BGM or CGM use is crucial during times of intercurrent illness to detect and prevent acute hyperglycemic complications such as DKA. Patients may also benefit from occasionally testing 2 hours after meals.[16]

Continuous glucose monitors report interstitial glucose levels in real-time and provide insight into glucose trends. Data from these devices can be used for insulin dose calculations, and some are integrated with insulin pumps. CGM use with intensive insulin therapy can reduce A1C, hypoglycemia, and glucose variability. Current guidelines support the use of CGM in patients on intensive insulin therapy. CGM is also recommended in patients with hypoglycemia unawareness to better detect and prevent hypoglycemic events.[30]

Diabetes Self-Management Education and Support (DSME/S)

Consistent, long-term diabetes control requires patients to have a good understanding of their disease and participate in routine self-management

strategies to control it. All patients should be offered access to diabetes self-management education and support (DSME/S) programs. There are four critical times to evaluate the need for DSME/S: at diagnosis, annually, when complicating factors arise, and when transitions in care occur.[29] The Association of Diabetes Care and Education Specialists (ADCES) has identified seven self-care behaviors that can be targeted through DSME/S. The behaviors include healthy eating, being active, monitoring, taking medications, problem-solving, reducing risk, and healthy coping.[31] The patient must be involved in the decision-making process and the process must be collaborative. Emphasize that complications can be prevented or minimized with good glycemic control and managing risk factors for ASCVD. Motivational interviewing techniques have been shown to be effective. Briefly, this involves asking open-ended questions that encourage patients to identify and acknowledge barriers that hinder achieving health goals, and then work to address them with the educator's guidance.

Health professionals with formal training and experience in diabetes education can become certified. A certified diabetes care and education specialist (CDCES) must document their experience providing patient education and pass a certification examination. An increasing number of nurses, pharmacists, dietitians, and physicians are becoming a CDCES. Formal diabetes education programs often employ several health professionals including a CDCES. Accredited diabetes education programs can receive payment through Medicare and private health insurance plans. The AADE and ADA accredit diabetes education programs. It must be noted, however, that there are not enough practitioners who hold the CDCES credential to provide education to all patients with diabetes. Therefore, all healthcare professionals must be well-versed in the educational needs related to diet, physical activity, and other self-care behaviors to provide education and reinforcement of these crucial management strategies. Finally, patients should be advised not to smoke, and smoking cessation counseling should be a routine component of diabetes care.

PHARMACOLOGIC THERAPIES

Insulin

Endogenously produced insulin is cleaved from the larger proinsulin peptide in the β-cell to the active peptide of insulin and inactive C-peptide. All commercially available insulin preparations contain only the active insulin peptide and are produced and manufactured exclusively using recombinant DNA technology. "Human" insulins (NPH, regular) are recombinant DNA–derived human insulin, while insulin analogs have had amino acids substitutions in the insulin molecule that change the onset or duration of action. Most insulin products are administered subcutaneously for the chronic management of diabetes, except for inhaled human insulin which is a dry powder of human recombinant DNA regular insulin that is inhaled and absorbed through pulmonary tissue. The main advantage of insulin over other antihyperglycemic agents is that it can achieve a wide range of glucose targets and the dose can be individualized based on glycemic levels. Disadvantages include the risk of hypoglycemia, the need for injection(s), weight gain, and treatment burden.

Insulin is available in several concentrations containing 100 units/mL (U-100), 200 units/mL (U-200), 300 units/mL (U-300), or 500 units/mL (U-500). The most commonly used insulin concentration is U-100. Concentrated insulins containing more than 100 units/mL may be considered for individuals that require larger doses of insulin.

The pharmacokinetics and pharmacodynamics of insulin products are characterized by the onset, peak, and duration of appearance and action (see Table 94-7). Absorption of insulin from a subcutaneous depot is dependent on several factors, including source of insulin, concentration of insulin, additives to the insulin preparations (eg, zinc and protamine), blood flow to the area (rubbing of injection area, increased skin temperature, and exercise in muscles near the injection site may enhance absorption), and injection site. The abdomen provides the most consistent absorption for insulin.

TABLE 94-7

Pharmacodynamics of Insulin Preparations

Preparations (U-100 Unless Otherwise Noted)	Onset	Peak[a]	Duration[a]
Ultra-rapid acting			
Insulin aspart (Fiasp)	15-20 min[b]	90-120 min	5-7 hr

Insulin lispro aabc (Lyumjev)	15-17 min[c]	120-174 min	4.6-7.3 hr
Insulin human—inhaled (Afrezza)	12 min	35-55 min	1.5-4.5 hr
Rapid-acting			
Insulin aspart (NovoLog)	10-20 min	30-90 min	3-5 hr
Insulin lispro U-100, U-200 (Humalog, Admelog)			
Insulin glulisine (Apidra)			
Short-acting			
Regular (Humulin R, Novolin R)	30-60 min	2-4 hr	5-8 hr
Intermediate-acting			
NPH (Humulin N, Novolin N)	2-4 hr	4-10 hr	10-24 hr
Regular U-500 (Humulin R 500)	15-30 min	4-8 hr	13-24 hr
Long-acting			
Insulin detemir (Levemir)	1.5-4 hr	6-14[d] hr	16-20 hr
Insulin glargine (Lantus, Basaglar)	2-4 hr	No peak	20-24 hr
Insulin glargine U-300 (Toujeo)	6 hr	No peak	36 hr
Insulin degludec U-100, U-200 (Tresiba)	1 hr	No peak	42 hr
Combination Products			
70% NPH/30% Regular (Humulin 70/30, Novolin 70/30)	30-60 min	Dual	10-16 hr
75% NPL, 25% lispro (Humalog 75/25)	5-15 min		10-16 hr
50% NPL, 50% lispro (Humalog 50/50)	5-15 min		10-16 hr
70% insulin aspart protamine, 30% insulin aspart (Novolog 70/30)	5-15 min		15-18 hr

NPH, neutral protamine Hagedorn; NPL, insulin lispro protamine suspension.

[a]The peak and duration of insulin action are variable, depending on the injection site, duration of diabetes, kidney function, smoking status, and other factors.

[b]Onset of appearance is 2.5 minutes compared to 5.2 minutes for insulin aspart (NovoLog).

[c]Onset of appearance is 1 minute.

[d]Long-acting insulins are considered "peakless," although they have exhibited peak effects during comparative testing.

Basal insulin, also called background insulin, refers to longer-acting insulins that regulate BG levels in between meals by suppressing hepatic glucose production and maintaining near-normal glycemic levels in the fasting state. Bolus insulin refers to short- or rapid-acting insulins that cover meals (also called prandial insulin) or glycemic excursions (also called correction insulin). Basal insulin is the preferred and most convenient initial insulin formulation in patients with type 2 DM while patients with type 1 DM require a combination of basal and bolus insulin to achieve adequate glycemic control.[32,33]

Basal insulin options include NPH, detemir, glargine U-100, glargine U-300, degludec U-100, or degludec U-200. From a pharmacokinetic/pharmacodynamic (PK/PD) perspective, NPH is the least ideal basal insulin as it has a distinct peak and a duration of action much less than 24 hours. While it can be given once daily in some patients with type 2 DM, it usually is dosed twice daily. Detemir also has a peak and often lasts less than 24 hours, but has a more ideal profile compared to NPH. It can be given once daily in some patients but should be dosed twice daily when low doses (less than 0.3 units/kg) are used. Insulin glargine U-100 offers a slightly better profile; it is considered to be peakless and can usually be given once daily. The longer-acting agents (glargine U-300 and degludec) have no peak and a longer duration of action compared to glargine U-100 and detemir. They are given once daily. It is important to consider whether these PK/PD differences translate into clinically meaningful differences in patient outcomes. Clinical trial evidence indicates that all basal insulins can achieve similar A1C reductions if dosed and titrated properly; but the longer-acting basal insulins have a lower risk of hypoglycemia, particularly nocturnal hypoglycemia, and may result in less glucose variability. They do, however, cost more, so the benefits and risks need to be considered on a patient-specific level.

Bolus insulin options include short-acting regular, rapid-acting insulins (aspart, lispro, and glulisine), and ultra-rapid insulins (inhaled human insulin, fast-acting insulin aspart [Fiasp], and insulin lispro aabc [Lyumjev]). Similar to basal insulins, the PK/PD profiles of bolus insulins have improved over time with the rapid-acting insulins offering a faster onset and shorter duration of action compared to regular insulin and the ultra-rapid insulins offering an even faster onset. Rapid and ultra-rapid acting agents may more closely mimic prandial endogenous insulin release. This is likely more relevant to patients with type 1 DM, where therapy is aiming to mimic a functioning pancreas that secretes insulin rapidly after a meal. Rapid-acting insulins have a modestly lower risk of hypoglycemia compared to regular insulin; however, efficacy can be achieved with all prandial insulins and the differences in cost can be substantial. Therefore, when selecting a bolus insulin, a patient-specific evaluation of the benefits and risks should be done.[32,33]

U-500 regular insulin is reserved for use in patients with extreme insulin resistance. It is most often given two or three times a day. To avoid medication errors, it is recommended to prescribe U-500 regular in a pen device or to use U-500 syringes if dispensing U-500 regular in a vial.

Various premixed insulin products, which contain both a basal and a prandial component, are also available and can offer an alternative for patients who require fewer injections or a simpler regimen. However, these products are limited by their fixed mixed formulations which can make tailoring the dosing regimen challenging.

Although endogenous hyperinsulinemia and insulin resistance have been associated with increased CV risk, exogenous insulin therapy has not been associated with increased adverse CV outcomes in several large-scale clinical trials.[17,20,34]

The most common adverse effect reported with insulin is hypoglycemia. It is more common in patients on intensive insulin therapy regimens. Patients with type 1 DM experience more hypoglycemic events when compared to type 2 DM patients who use insulin. In the UKPDS study, the percentage of type 2 DM patients who needed third-party assistance due to a severe hypoglycemic reaction was 2.3%.[20] In the DCCT study, intensive glycemic control increased the risk of severe hypoglycemia threefold when compared to conventional therapy in patients with type 1 DM.[17] Insulin use is associated with

an increased risk of hospitalizations in older adults based on public health surveillance data.[35]

Insulin also causes dose-dependent weight gain, which predominantly occurs in truncal fat. Weight gain can be minimized by using physiologic insulin replacement strategies or combining insulin therapy with other medications that mitigate weight gain or promote weight loss.

Insulin can cause injection site reactions including redness, pain, itching, urticaria, edema, and inflammation. Administration of insulin subcutaneously can result in lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients. Lipohypertrophy is caused by repeated injections into the same injection site. Due to insulin's anabolic actions, fat accumulates at the injection site and absorption at this site becomes variable. Lipoatrophy, in contrast, is due to insulin antibodies or allergic-type reactions that destroy the fat at the site of injection. Routinely rotating injection sites prevents these problems from developing and, when lipodystrophy is detected, the injection site should be avoided.

Concerns have been raised about a potential risk of cancer with insulin glargine, but trial results have been conflicting. While some studies using administrative data have found an association between insulin glargine and cancer, other meta-analyses and prospective studies have not.[34]

Inhaled human insulin can cause cough and upper respiratory infections and its use in chronic obstructive pulmonary disease and asthma is contraindicated due to bronchospasm risk. Inhaled insulin use has been associated with a small decline in pulmonary function and patients should have spirometry tests performed at baseline, 6 months, and annually thereafter. If a 20% reduction or greater in forced expiratory volume in 1 second is observed, inhaled insulin should be discontinued.

Insulin is degraded in the liver, muscle, and kidney. Liver deactivation is 20% to 50% in a single passage through the liver. Approximately 15% to 20% of insulin metabolism occurs in the kidney. This may explain the lower insulin dosage requirements and longer duration of activity observed in patients with ESKD.

The dose of insulin must be individualized. In type 1 DM, the average daily requirement for insulin is 0.5 to 0.6 units/kg, with approximately 50% being delivered as basal insulin, and the remaining 50% dedicated to meal coverage. During the honeymoon phase, it may fall to 0.1 to 0.4 units/kg. During acute illness or with ketosis or states of relative insulin resistance, the need for higher dosages is common. In type 2 DM, a higher dosage is required for those patients with significant insulin resistance. Dosages vary widely depending on the degree of insulin resistance and concomitant antihyperglycemic medication use. More specific information on insulin dosing is included in the "General Approach to Hyperglycemia Management" section.

The effectiveness of insulin is highly dependent on its appropriate use. Product selection, education and training, and reinforcement are crucial. Counseling must include proper administration (including dose, injection technique, and timing of injection), glycemic targets, BGM, dose titration or adjustment, storage, and prevention, detection, and treatment of hypoglycemia. Each insulin product is unique in the delivery device used. Some insulin products are available in vials, disposable pen devices, or pen cartridges, but many newer insulins are only available in pen devices. Each pen device product has different quantities, maximum injection doses, storage requirements, and expirations. NPH insulin and all suspension-based insulin preparations should be inverted or rolled gently at least 20 times to fully suspend the insulin prior to each use. Improper mixing of the suspension prior to administration can lead to glycemic variability. Pharmacists should review recent guidelines on proper injection technique and prescribing information for specific products prior to counseling patients and utilize reliable, up-to-date patient education resources to ensure product-specific, accurate counseling information.[36,37]

Biguanides

Metformin is the only biguanide available in the United States. It is oral and available as an immediate-release formulation that is dosed twice daily or an extended-release (XR) formulation that is dosed once or twice daily (Table 94-8). Its mechanism of action in terms of glucose-lowering are complex and not yet fully understood. At the cellular level, metformin activates AMP kinase. Metformin has been shown to decrease hepatic glucose production, yet not all of its effects can be explained by that mechanism and there is increasing evidence of mechanisms in the gut. Additionally, metformin's effects may be partially related to enhanced insulin sensitivity in peripheral (muscle) tissues, which allows for an increased uptake of glucose into muscle cells. Metformin has no direct effect on the β-cell, but insulin concentrations are reduced due to improved insulin sensitivity.[38]

TABLE 94-8

Dosing Recommendations for Oral Medications Used to Treat Type 2 Diabetes

Generic Name	Starting Dose	Usual Recommended Dose	Maximal Dose (mg/day)	Dosing/Use Based on Kidney Function[a]
Biguanides				
Metformin	500 mg once or twice daily or 850 mg once daily, titrate to target dose as tolerated	1,000 mg twice daily	2,550	Do not initiate if eGFR 30-45; Do not use if eGFR<30
Metformin XR	500 mg to 1,000 mg once daily, titrate to target dose as tolerated	2,000 mg once daily	2,500	Do not initiate if eGFR 30-45; Do not use if eGFR<30
Sodium-glucose co-transporter (SGLT)-2 inhibitors				
Canagliflozin	100 mg once daily	100-300 mg once daily	300	100 mg once daily if eGFR 30-60; Do not initiate if eGFR <30
Dapagliflozin	5 mg once daily[b]	5-10 mg once daily	10	Not recommended for glycemic control if eGFR <45[c]; Do not initiate if eGFR <25
Empagliflozin	10 mg once daily	10-25 mg once daily	25	Not recommended if eGFR <45
Ertugliflozin	5 mg once daily	5-15 mg once daily	15	Do not initiate if eGFR <60; Do not use if eGFR <30
Dipeptidyl peptidase (DPP)-4 inhibitors				
Alogliptin	25 mg once daily	25 mg once daily	25	12.5 mg once daily if CrCl 30-60 mL/min (0.5-1.0 mL/s); 6.25 mg once daily if CrCl <30 mL/min (0.5 mL/s)
Linagliptin	5 mg once daily	5 mg once daily	5	No dose adjustment needed
Saxagliptin	2.5-5 mg once daily	5 mg once daily	5	2.5 mg once daily if eGFR ≤50
Sitagliptin	100 mg once daily	100 mg once daily	100	50 mg once daily if eGFR 30-50 25 mg once daily if eGFR <30
Thiazolidinediones (TZD)				
Pioglitazone	15 mg once daily	30 mg once daily	45	No dose adjustment required
Rosiglitazone	4 mg once daily or in two divided doses	4 mg once daily or in two divided doses	8	No dose adjustment required
Sulfonylureas (first generation)				
Chlorpropamide	250 mg once daily (100 mg once daily in	100-500 mg once	750	Consider alternative agent or initiate

	older adults)	daily		conservatively at 100 mg in kidney insufficiency to avoid hypoglycemia
Tolazamide	250 mg once daily (100 mg once daily in older adults or if FPG <200 mg/dL [11.1 mmol/L])	250-500 mg once daily	1,000	Consider alternative agent or initiate conservatively at 100 mg in kidney insufficiency to avoid hypoglycemia
Tolbutamide	1,000-2,000 mg once daily (250-500 mg once daily in older adults)	1,000-2,000 mg once daily	3,000	Consider alternative agent or initiate conservatively in kidney insufficiency to avoid hypoglycemia
Sulfonylureas (second generation)				
Glimepiride	1-2 mg once daily (1 mg once daily in older adults)	4 mg once daily	8	Initiate conservatively at 1 mg in kidney insufficiency to avoid hypoglycemia
Glipizide Glipizide XL	5 mg once daily (2.5 mg daily in older adults)	5-10 mg once daily	20	Initiate conservatively at 2.5 mg in kidney insufficiency to avoid hypoglycemia
Glyburide	2.5-5 mg once daily (1.25 mg once daily in older adults)	5-10 mg once daily	20	Consider alternative agent or initiate conservatively at 1.25 mg in kidney insufficiency to avoid hypoglycemia
Glyburide micronized	1.5-3 mg once daily (0.75 mg once daily in older adults)	3-6 mg once daily	12	Consider alternative agent or initiate conservatively at 0.75 mg in kidney insufficiency to avoid hypoglycemia
Meglitinides				
Nateglinide	120 mg three times daily before meals	120 mg three times daily before meals	360	No adjustment required
Repaglinide	1-2 mg three times daily before meals (0.5 mg before meals if A1C<8% [0.08; 64 mmol/mol])	2-4 mg three times daily before meals	16	Initiate conservatively at 0.5 mg before meals if CrCl 20-40 mL/min (0.33 to 0.67 mL/s)
α-Glucosidase inhibitors				
Acarbose	25 mg once to three times daily with meals	50 mg once to three times daily with meals	300	Avoid if CrCl <25 mL/min (0.42 mL/s)
Miglitol	25 mg once to three times daily with meals	50 mg once to three times daily with meals	300	Avoid if CrCl <25 mL/min (0.42 mL/s)
Bile acid sequestrants				
Colesevelam	1.875 g twice daily or 3.75 g once daily	1.875 g twice daily or 3.75 g once daily	3.75 g/day	No dose adjustment needed

Dopamine agonists				
Bromocriptine	0.8 mg once daily	1.6-4.8 mg once daily	4.8	No dose adjustment needed

[a]eGFR units: mL/min/1.73 m^2.

[b]For indications other than glycemic control; the recommended starting dose is 10 mg.

[c]For indications other than glycemic control: 10 mg for eGFR >25; if eGFR <25 patients may continue until dialysis but initiation is not recommended.

Metformin has historically been the drug of choice for glucose lowering in patients with type 2 DM due to extensive experience, high efficacy, minimal hypoglycemia risk, positive or neutral effects on weight, potential positive impact on CV risk, manageable side-effect profile, and low cost. Metformin is often used in combination with other treatments and current treatment guidelines recommend continuing metformin unless a contraindication or intolerability exists.[32,33] Metformin consistently reduces A1C levels by 1.5% to 2.0% (0.015 and 0.020; 16 and 22 mmol/mol) and FPG levels by 60 to 80 mg/dL (3.3-4.4 mmol/L) in drug-naïve patients with A1C values of approximately 9% (0.09; 75 mmol/mol). Metformin does not cause weight gain, and may actually lead to a modest (2-3 kg) weight loss. Since metformin does not directly increase insulin secretion from the pancreas, it has a low risk of hypoglycemia. Metformin also has positive effects on several components of the insulin resistance syndrome. Metformin decreases plasma triglycerides and low-density lipoprotein cholesterol (LDL-C) by approximately 8% to 15% and modestly increases high-density lipoprotein cholesterol (HDL-C) by 2%.

Metformin reduced the composite of all diabetes-related endpoints by 32%, diabetes-related death by 42%, and all-cause mortality by 36% in overweight subjects in the UKPDS compared to conventional treatment. Intensive treatment with metformin was also significantly better than intensive treatment with sulfonylureas or insulin at reducing any diabetes-related endpoint, all-cause mortality, and stroke. However, meta-analyses have not confirmed these benefits.[21,39,40] Metformin frequently causes GI side effects, including diarrhea, abdominal discomfort, and/or stomach upset. These side effects are usually dose-dependent, transient, mild in nature, and can be minimized with slow dose titration. Patients should take metformin with or immediately after meals. When initiating therapy, it is important to use a low dose, typically 500 mg given with the largest meal, to minimize GI adverse effects. The dose is then increased in 500 mg increments over several weeks. Approximately 5% to 10% of patients cannot tolerate metformin despite the slow dose titration. Extended-release metformin may lessen some of the GI side effects, but a recent head-to-head comparison of immediate-release versus extended-release metformin found no significant differences in rates of GI adverse effects.[41]

Metformin may cause a metallic taste, due to metformin in salivary secretions and may lower vitamin B_{12} concentrations. Therefore, B_{12} levels or methylmalonic acid should be measured annually or if a deficiency is suspected. Peripheral neuropathy, a microvascular complication that is common in diabetes, could manifest or worsen with B_{12} deficiency. Vitamin B_{12} supplementation by sublingual, oral, or injection easily treats this deficiency.

Rare cases of lactic acidosis have been reported with metformin, usually in the setting of severe illness or acute kidney injury. The risk appears to be exceedingly small but may increase in patients with moderate-to-severe kidney insufficiency or tissue hypoperfusion states such as acute congestive heart failure, excessive alcohol intake, and hepatic impairment. The clinical presentation of lactic acidosis is often nonspecific flu-like symptoms. The diagnosis is therefore made by laboratory confirmation of high lactic acid levels and acidosis.

Metformin can be used in combination with any other antihyperglycemic therapy and is often continued when insulin therapy is initiated. The target dose for metformin is 1,000 mg twice daily or 2,000 mg daily if the extended-release product is used. The minimal effective dose of metformin is 1,000 mg/day (Table 94-8). Approximately 80% of the glycemic-lowering effect may be seen at 1,500 mg daily.

Metformin is renally excreted and accumulates in patients with kidney insufficiency; therefore, metformin is contraindicated in patients with an eGFR <30 mL/min/1.73 m^2 and should be used with caution in patients with milder kidney insufficiency. Initiation of metformin is not recommended in patients with an eGFR 30 to 45 mL/min/1.73 m^2 but can be continued with increased kidney function monitoring; a dose reduction of 50% of maximal dose may be warranted.[42–44] Due to the risk of acute kidney failure when IV contrast dye is used during imaging procedures, metformin therapy should be withheld starting the day of the procedure and resumed 2 to 3 days later, if normal kidney function has been documented. It need not be withheld

for days prior to the procedure.

Sodium-Glucose Co-transporter-2 Inhibitors

Four SGLT-2 inhibitors have been approved by the FDA including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, all of which are oral, once-daily products. SGLT-2 inhibitors reduce plasma glucose by preventing the kidneys from reabsorbing glucose back into the bloodstream, leading to increased glucose excretion in the urine. By inhibiting SGLT-2, the renal tubular threshold for glucose reabsorption is lowered and glucosuria occurs at lower levels of plasma glucose concentrations. SGLT-2 inhibition lowers BG through an insulin-independent mechanism and exerts its glucose-lowering effect whenever the plasma glucose is elevated. Thus, SGLT-2 inhibitors can lower both FPG and PPG and are effective even in the absolute absence of insulin. Although SGLT-2 inhibitors block the reabsorption of 90% of the filtered glucose load, which could theoretically result in up to 170-g loss of glucose/day in the urine, urinary glucose excretion (UGE) does not exceed 75 to 85 g/day, because SGLT-1 begins to compensate and can reabsorb up to 30% to 40% of the filtered glucose load, when working at maximal capacity. Thus, when SGLT-2 is inhibited, SGLT-1 instantaneously can augment its reabsorption of glucose and blunt the glucosuric effect of the SGLT-2 inhibitor.

The SGLT-2 inhibitors are considered to have intermediate A1C-lowering efficacy and reduce A1C by 0.5% to 1% (0.005 to 0.01; 6 to 11 mmol/mol). They appear to be more efficacious in patients with higher baseline A1C levels. As eGFR declines, the amount of glucose that reaches the proximal tubule declines; thus, kidney impairment decreases the glucose-lowering efficacy of SGLT-2 inhibitors. Increased UGE leads to the loss of 200 to 300 kcal/day (840 to 1,300 kJ/day), which may contribute to 1 to 5 kg of weight loss. The filtering of more glucose in the urine also causes an osmotic diuresis effect that can result in modest reductions in systolic BP by 3 to 4 mm Hg and diastolic BP by 1 to 2 mm Hg. Because of the insulin-independent mechanism, SGLT-2 inhibitors are unlikely to cause hypoglycemia unless combined with medications such as sulfonylureas, meglitinides, or insulin.

The SGLT-2 inhibitors have additional benefits related to improving CV, HF, and CKD outcomes. Large-scale, CV outcome trials have been completed for empagliflozin, canagliflozin, and dapagliflozin. Both empagliflozin and canagliflozin demonstrated benefit at reducing major adverse CV events (myocardial infarction, stroke, or CV death) in patients with type 2 DM and established CVD or high CV risk.[45–47] Secondary endpoints of HF hospitalizations and worsening nephropathy were also reduced in these studies. Dapagliflozin was noninferior (but not superior) to placebo at reducing major adverse CV events in patients with type 2 DM who had or were at risk for ASCVD. There was a significant reduction in the composite endpoint of heart failure hospitalizations or CV death with dapagliflozin compared to placebo, and a reduction in the progression of kidney disease.[48] Additional outcome trials have provided primary outcomes evidence demonstrating a significant benefit from dapagliflozin and empagliflozin at reducing the risk of worsening heart failure or CV death in patients with heart failure, with or without type 2 DM[49,50] and the benefit from dapagliflozin at reducing the risk of adverse kidney-related outcomes in patients with CKD with or without type 2 DM.[51] There is also primary outcome evidence demonstrating kidney benefit of canagliflozin in patients with CKD and type 2 DM.[52,53] Due to these benefits, the SGLT-2 inhibitors have expanded FDA indications beyond glucose-lowering (Table 94-9).

TABLE 94-9

SGLT-2 Inhibitors and GLP-1 Receptor Agonists with FDA Indications Beyond Glycemic Control[a]

Drug Name	FDA Indications Beyond Glycemic Control
SGLT-2 inhibitors	
Canagliflozin	• to reduce the risk of major adverse CV events in adults with type 2 DM and established CVD • to reduce the risk of ESKD, doubling of serum creatinine, CV death, and hospitalization for HF in adults with type 2 DM and diabetic nephropathy with albuminuria
Dapagliflozin	• to reduce the risk of hospitalization for HF in adults with type 2 DM and either established CVD or multiple CV risk factors • to reduce the risk of CV death and hospitalization for HF in adults with HF with reduced ejection fraction (NYHA class II-IV) • to reduce the risk of sustained eGFR decline, ESKD, CV death and hospitalization for HF in adults with CKD at risk of progression
Empagliflozin	• to reduce the risk of CV death in adult patients with type 2 DM and established CVD • to reduce the risk of CV death and hospitalization for heart failure in adults with heart failure
GLP-1 receptor agonists	
Dulaglutide	• to reduce the risk of major adverse CV events in adults with type 2 DM who have established CVD or multiple CV risk factors
Liraglutide	• to reduce the risk of major CV events such as heart attack, stroke, or death in adults with type 2 DM with known heart disease • as an adjunct to diet and physical activity for chronic weight management in adult patients with a BMI) of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 or greater in the presence of at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia)
Semaglutide (SC)	• to reduce the risk of major adverse CV events (CV death, nonfatal myocardial infarction or nonfatal stroke) in adults with type 2 DM and established CVD • for chronic weight management as an adjunct to diet and physical activity in adults with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of a weight-related comorbidity, and pediatric patients aged 12 years and older with an initial BMI at ≥95th percentile for age and sex.

For glycemic control, the SGLT-2 inhibitors can be added to metformin or used in combination with other second-line agents. They can be used as monotherapy in patients who cannot tolerate or take metformin. They are recommended by the ADA guidelines for many patient populations including those with indicators of high risk or established ASCVD, HF, or CKD. For patients with those comorbidities, SGLT-2 inhibitors should be considered independently of baseline A1C, individualized A1C target, or metformin use. The SGLT-2 inhibitors are also recommended for those with a compelling need to avoid hypoglycemia or a compelling need to avoid weight gain or induce weight loss.

Excess glucose in the urine is responsible for causing genital mycotic infections, the most common side effect of the SGLT-2 inhibitors. There is also a slightly increased risk of urinary tract infections. Genitourinary (GU) infections occur more frequently in women and uncircumcised men. In clinical trials, GU infections led to discontinuation in less than 1% of patients; most GU infections were treated and patients were able to continue the SGLT-2 therapy. Patients should be educated about the signs and symptoms of GU infections and the importance of proper personal hygiene.

SGLT-2 inhibitors can also cause polyuria, dehydration, dizziness, or hypotension due to the osmotic diuresis effects. Symptomatic hypotension may occur more frequently in patients with low baseline BP or an eGFR less than 60 mL/min/1.73 m^2. Concomitant diuretic use may increase the risk of orthostatic hypotension and electrolyte abnormalities. Patients should be monitored carefully and dose or drug therapy adjustments may be needed. Older adults and patients with stage 4 or 5 CKD are not optimal candidates for SGLT-2 inhibitors. Older adults typically have diminished kidney function and, because they may have poor thirst response, they are predisposed to dehydration. The mechanism of action and osmotic diuresis with SGLT-2 inhibitors may affect several laboratory tests. LDL-C and HDL-C increase slightly with SGLT-2 inhibitors. Hemoconcentration from diuresis can result in a 2% to 3% increase in hematocrit. Urinalysis will always be positive for glucose due to the mechanism of action.

Other safety concerns that have been raised since SGLT-2 inhibitors have come to market include ketoacidosis, amputations, fractures, and Fournier gangrene. Several cases of ketoacidosis have been reported and meta-analyses have shown a small increased risk, although absolute numbers are small. Unlike the typical presentation of DKA, SGLT-2 inhibitor-related ketoacidosis presents uniquely, in that glucose levels typically do not go over 250 mg/dL (13.9 mmol/L) because of the increased UGE. Most cases have been in patients with type 1 DM, thus the SGLT-2 inhibitors are not currently approved by the FDA in this population. Insulin-deficient patients (those with type 1 DM, LADA, or insulin-requiring type 2 DM) are at the highest risk, especially in the setting of decreased insulin use, increased insulin needs (acute illness or infection, surgery, trauma), or low-carbohydrate intake or dehydration. Patients should be well hydrated prior to treatment initiation, temporarily stop the drug if a serious illness is encountered, and should not decrease the insulin dose prospectively when it is initiated.

Canagliflozin was associated with an increased risk of bone fracture and lower-limb amputations in its large CV outcome trial. Many of the fractures were distal fractures of the upper extremities after a fall, and thus may be related to dizziness and orthostatic hypotension. Amputations are more common in patients with peripheral neuropathy, peripheral vascular disease, or prior amputations, so caution should be used in this patient population when considering SGLT-2 inhibitor therapy.

The use of SGLT-2 inhibitors has been associated with Fournier gangrene, a rare urological emergency characterized by necrotizing infection of the external genitalia, perineum, and perianal region. To date, 55 cases have been reported and, thus, causality has not been established.[54]

The SGLT-2 inhibitors should be initiated at a low dose. Volume status, adverse effects, and kidney function should be assessed. The dose may be titrated in patients who are tolerating the drug well and require additional glucose control. Since the glucose-lowering effect of these medications is dependent on kidney function, it is not recommended to start or continue SGLT-2 therapy for the purpose of glucose-lowering when the eGFR is consistently less than 45 mL/min/1.73 m^2, although these medications can be used for alternative indications at lower eGFR levels. Use and dose recommendations vary between agents for patients with kidney dysfunction (Table 94-8).

Glucagon-Like Peptide-1 Receptor Agonists

Currently there are six GLP-1 RAs and one dual GLP-1/GIP RA available in the United States. These products are administered either subcutaneously or orally with dosing schedules ranging from twice daily to once weekly (Table 94-10). The class mimics the action of endogenous GLP-1 and GIP. They stimulate insulin secretion from pancreatic β-cells in a glucose-dependent manner. In addition, during hyperglycemia, GLP-1 RAs reduce inappropriately elevated levels of glucagon, which results in decreased hepatic glucose output. These agents also have a direct effect on the stomach through the autonomic nervous system to slow gastric emptying, thereby reducing meal-related glucose excursions. Additionally, agents that penetrate the blood-brain barrier increase satiety via the central nervous system. These actions result in a reduction in both glucose and weight. GLP-1 RAs also potentially preserve pancreatic β-cell function and protect against cytokine-induced apoptosis. All GLP1 RAs result in pharmacologic levels of GLP-1 and are resistant to the rapid degradation by the dipeptidyl peptidase 4 (DPP-4) enzyme.

TABLE 94-10

Clinical Comparisons of GLP-1 Receptor Agonists

Generic Name	Primary Glucose Profile Target	Dose/Route	Interval	Dose/Use Based on Kidney Function	Availability, Storage, Preparation

Exenatide	PPG	5-10 mcg SC	Twice daily (within 60 minutes before breakfast and dinner)	Avoid if CrCl[a] <30 (0.5 mL/s); Use caution when initiating or increasing dose if CrCl 30-50 (0.5-0.83 mL/s)	• Multidose pens (5 mcg/dose, 10 mcg/dose, 60 doses per pen) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 30 days after first use
Lixisenatide	PPG	10-20 mcg SC	Once daily (1 hr before breakfast)	Limited experience in severe kidney impairment; avoid if eGFR <15[b]	• Multidose pen (10 mcg, 20 mcg, 14 doses per pen) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 14 days after first use
Dulaglutide	FPG and PPG	0.75-4.5 mg SC	Once weekly	Use with caution in patients with ESKD	• Single-dose pen (0.75 mg, 1.5 mg, 3.0 mg, 4.5 mg) • Pen needle attached • Keep refrigerated • May store at room temperature for 14 days
Exenatide XR	FPG and PPG	2 mg SC	Once weekly	Limited experience in severe kidney impairment; not recommended if eGFR or CrCl <30 (0.5 mL/s); Use with caution if CrCl 30-50 (0.5-0.83 mL/s)	• Single-dose pen (2 mg) • Pen needle supplied with pen • Keep refrigerated; may store at room temperature for 4 weeks • Store flat in original packaging, protected from light • Remove from refrigerator 15 minutes prior to mixing • Requires reconstitution; administer dose immediately once reconstituted
Liraglutide	FPG and PPG	0.6-1.8 mg SC	Once daily	Limited experience in ESKD	• Multidose pen (6 mg/mL, 3 mL; each pen delivers doses of 0.6, 1.2, or 1.8 mg) • Pen needles not supplied with pen • Keep refrigerated • After first use, store at room temperature; discard 30 days after first use
Semaglutide	FPG and PPG	0.25-1 mg SC	Once weekly	No dose adjustment recommended	• Multidose pen (low dose pen: 1.34 mg/mL, 2 mg/1.5 mL, delivers 0.25 mg or 0.5 mg doses; high-dose pen: 1.34 mg/mL, 4 mg/3 mL, delivers 1 mg dose) • Pen needles supplied with pen

					• Keep refrigerated • After first use, store at room temperature; discard 56 days after first use
Semaglutide	FPG and PPG	3-14 mg orally	Once daily	No dose adjustment recommended	• Store at room temperature • Should be taken 30 minutes before first food, beverage, or other medication of the day with no more than 4 ounces of water
Tirzepatide (GLP-1/GIP RA)	FPG and PPG	2.5-15 mg SC	Once weekly	No dose adjustment recommended	Single-dose pens (various doses) Keep refrigerated; may store at room temperature for up to 21 days

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FPG, fasting plasma glucose; PPG, postprandial glucose; SC, subcutaneous.

[a]CrCl units: mL/min.

[b]eGFR units: mL/min/1.73 m^2.

The A1C-lowering efficacy with GLP-1 RAs is considered high but depends on baseline glycemic control, background therapy, and the specific agent used. GLP-1 RAs can also lead to weight loss. The average weight loss is about 1-10 kg with GLP-1 RAs but is highly dependent on the specific agent and dose used, with clinical trial results varying from an average 0.3 kg weight gain to as much as a 23.6 kg weight loss when used at high doses.[55]

Currently, available GLP-1 RAs include dulaglutide, exenatide, exenatide XR, lixisenatide, liraglutide, and semaglutide (in both an injectable and oral formulation), and the dual GLP-1/GIP RA tirzepatide. Multiple differences exist in the characteristics of the individual agents within the class, including molecular structure and size, half-life, duration of action, ability to penetrate different tissue compartments, and homology to native GLP-1, which, in turn, lead to important clinical differences in efficacy, rates of adverse effects, dosing schedules, and impact on glucose profile (Table 94-10). Short-acting agents (exenatide and lixisenatide) predominantly lower PPG levels, likely due to their effect on gastric emptying. Long-acting agents (dulaglutide, liraglutide, exenatide XR, and semaglutide) lower both FPG and PPG, but demonstrate larger effects on FPG levels, due to their longer half-life and resultant suppression of glucagon overnight. Based on several head-to-head trials comparing specific agents to each other, dulaglutide, liraglutide, semaglutide, and tirzepatide have the highest A1C-lowering efficacy while exenatide and lixisenatide have the lowest.[56] Tirzepatide appears to have the highest weight loss efficacy, followed by semaglutide, liraglutide, dulaglutide, exenatide, and lixisenatide.[55,57,58]

The GLP-1 RAs have additional benefits related to improving CV and CKD outcomes. Large-scale CV outcome trials have been completed for dulaglutide, exenatide XR, lixisenatide, liraglutide, and semaglutide (SC). Both lixisenatide and exenatide XR demonstrated CV safety but did not reduce the rate of major adverse CV events (myocardial infarction, stroke, or CV death). Liraglutide, semaglutide, and dulaglutide, however, not only demonstrated CV safety but also demonstrated benefit at reducing the risk of major adverse CV events (myocardial infarction, stroke, or CV death) in patients with type 2 DM and established CVD or high CV risk.[45,59–61] The secondary endpoint of worsening nephropathy was also reduced in these studies. Due to these benefits, some GLP-1 RAs have expanded FDA indications beyond glucose-lowering (Table 94-9).

For glycemic control, the GLP-1 RAs are treatment options at multiple time points in the type 2 DM treatment algorithm and can be used in combination with many other agents including metformin, sulfonylureas, SGLT-2 inhibitors, and basal insulin. They can be used as monotherapy in patients who cannot tolerate or take metformin. They are recommended for many patient populations including those with indicators of high risk or established ASCVD or CKD, and those with a compelling need to avoid hypoglycemia or a compelling need to avoid weight gain or induce weight loss. They should not be used in combination with DPP-4 inhibitors due to the similar mechanisms of action. A significant amount of evidence shows the beneficial effect

of the combination of GLP-1 RA and a basal insulin.

The most common adverse effects associated with GLP-1 RAs are GI in nature, including nausea, vomiting, and diarrhea. These adverse effects appear to be dose-related so dose titration is recommended. They usually occur early in the treatment course, are typically mild in nature, and transient. Occasionally, the GI side effects are significant enough to require discontinuation. Long-acting preparations tend to have less impact on gastric emptying, and thus a slightly lower risk of nausea, compared to short-acting agents. Patients should be instructed to eat slowly and stop eating when satiated otherwise nausea may worsen or cause vomiting.

GLP-1 RAs enhance insulin secretion in a glucose-dependent manner in response to food intake; thus, the risk of hypoglycemia is low when combined with metformin, DPP-4 inhibitors, SGLT-2 inhibitors, or a TZD. However, when combined with a sulfonylurea or insulin, hypoglycemia may occur.

Antibody formation to GLP-1 RAs may occur, which could potentially attenuate the glycemic-lowering effects. Antibody formation is more likely to occur with exendin-4-based agents (exenatide, exenatide XR, and lixisenatide) than with other agents. Injection site reactions have also been reported in patients taking injectable GLP-1 RAs. These reactions may be more common in patients with high antibody titers. Exenatide XR can also cause injection site nodules, likely due to its formulation. It is encapsulated in microspheres made of a biodegradable polymer, which releases the drug over a sustained time interval. The microspheres can lead to injection site nodules described as pea-sized, hard, subcutaneous, lumps, masses, or induration. Hypersensitivity reactions, including anaphylaxis and angioedema, have also been reported with most GLP-1 RAs.

GLP-1 RAs have been associated with cases of acute pancreatitis, but no causal relationship has been established. While additional study is needed, it should be noted that (1) patients with type 2 DM are at inherently higher risk for developing pancreatitis; (2) GLP-1 RAs may mask the initial signs of pancreatitis, including nausea, vomiting, and abdominal pain; and (3) large studies have not linked GLP-1 RA use to a higher incidence of acute pancreatitis. In a patient with a history of pancreatitis, the benefits must be weighed against the potential risks. A GLP-1/GIP RA should not be used in patients with chronic pancreatitis. If a patient reports abdominal pain, nausea, and repeated vomiting, it is best to discontinue therapy temporarily and confirm that the symptoms are not a sign of a more serious underlying problem. GLP-1 RAs have not been studied in patients with gastroparesis, but since they delay gastric emptying they are not recommended in this patient population.

Long-acting GLP-1 RAs are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 due to a risk of medullary thyroid carcinoma. This contraindication is based on rodent model data that reported a higher risk of C-cell tumors of the thyroid but has not been seen in humans. Rodents may not be the ideal model to study this effect as they express a high number of GLP-1 receptors on thyroid C-cells. The expression of GLP-1 receptors in the thyroid of humans is minimal. Rodents also have a higher baseline prevalence of C-cell tumors compared to humans. There is no contraindication in patients with a history of other types of thyroid cancers.

Most GLP-1 RAs require subcutaneous administration into the abdomen, thigh, or upper arm. Each agent uses a unique injection pen device with unique administration requirements; patients must be instructed on how to use the specific product they have been prescribed. The short-acting agents have specific timing requirements in relation to meals since their mechanisms are more targeted toward slowing gastric emptying postprandially. If the dose of exenatide or lixisenatide is missed, it should not be taken after the meal. The long-acting agents have more flexibility with the timing of doses and can be taken at any time of day, with or without food. Oral semaglutide should be taken 30 minutes before the first food, beverage, or other medication of the day with no more than 4 ounces of water. Most of the GLP-1 RAs (except for exenatide XR) have recommended lower doses when initiating the drug, followed by titration to higher doses if needed for glycemic control. This is to minimize GI adverse effects since the GI adverse effects are dose-related and transient. For the once-weekly agents, steady state is attained at 6 to 8 weeks. For GLP-1 RAs administered weekly, if a dose is missed it should be taken as soon as possible but not within 3 days of the next dose. Use caution when starting or increasing the dose of GLP-1 RAs in patients with kidney insufficiency as there have been case reports of acute kidney injury or worsening kidney function. Most occurred in patients who experienced nausea, vomiting, diarrhea, or dehydration. Exenatide and exenatide XR should be avoided in patients with eGFR<30 mL/min/1.73 m^2, and lixisenatide should be avoided in patients with eGFR <15 mL/min/1.73 m^2.

Dipeptidyl Peptidase-4 Inhibitors

Four DPP-4 inhibitors are approved by the FDA: sitagliptin, saxagliptin, linagliptin, and alogliptin, all of which are oral, once-daily products. These agents inhibit the DPP-4 enzyme responsible for the rapid degradation of GLP-1 and GIP, thereby prolonging the half-life of endogenously produced GLP-1 and GIP. Levels of GLP-1 are deficient in patients with type 2 DM. As these agents block nearly 100% of the DPP-4 enzyme activity for at least 12 hours, normal physiologic, GLP-1 levels are achieved. This leads to an increase in glucose-dependent insulin secretion from the pancreas and a

reduction in inappropriate postprandial glucagon secretion, resulting in lower glucose levels without an increase in hypoglycemia when used as monotherapy. These drugs do not alter gastric emptying and do not cause nausea or have significant effects on satiety. DPP-4 inhibitors have a neutral impact on weight.

The DPP-4 inhibitors have moderate glucose-lowering efficacy, with an average reduction in A1C of 0.5% to 0.9% (0.005-0.009; 6-10 mmol/mol) when used at maximum doses. DPP-4 inhibitors have a shallow dose-response curve. There are no clear differences in efficacy between medications within the class. DPP-4 inhibitors are considered second- or third-line therapy in the ADA algorithm, particularly when there is a compelling need to minimize hypoglycemia or weight gain, but they have less A1C-lowering efficacy compared to other medication classes. Potential advantages of the DPP-4 inhibitors include once-daily dosing, oral administration, weight neutrality, low risk of hypoglycemia, and good tolerability. They may be used in older adults with moderate-to-severe kidney insufficiency or those where drug tolerability is a priority. However, their ability to lower BG is modest and they are expensive.

The DPP-4 inhibitors are extremely well-tolerated. Adverse effects are uncommon but could include stuffy, runny nose; headache; or upper respiratory tract infections. Safety concerns that have arisen post-market with the DPP-4 inhibitors include heart failure, pancreatitis, and joint pain. The CV outcome trials with saxagliptin, sitagliptin, linagliptin, and alogliptin all demonstrated the overall CV safety of these agents, with no significant differences in major CV outcomes compared with placebo.[45] However, an increased risk of heart failure hospitalizations with saxagliptin compared with placebo reached statistical significance, and there was a trend toward increased heart failure hospitalizations with alogliptin compared with placebo.[45,62] Because of these findings, prescribing information for both saxagliptin and alogliptin includes information about the increased risk of hospitalization for heart failure, particularly in patients with existing heart or kidney disease. Patients taking these medications should contact their health professional if they develop signs and symptoms of heart failure, and providers should consider discontinuing the medication in patients who develop heart failure.

The FDA has also issued a warning on the risk of severe joint pain with DPP-4 inhibitors. This warning was based on 33 cases between 2006 and 2013. The joint pain occurred between 1 day to years after initial use, and symptoms were relieved after discontinuation of the DPP-4 inhibitor. Patients should not stop taking the drug if symptoms occur but should contact their health professional.

Similar to the GLP-1 RA class, there have been reports of increased risk of pancreatitis with DPP-4 inhibitors, but a causal relationship has not been established and individual, large, prospective studies have not shown an increased risk. A meta-analysis did show a small but statistically significant increased risk of pancreatitis with DPP-4 inhibitor use compared with placebo showing one to two cases of acute pancreatitis for every 1,000 patients treated for 2 years. Thus, pancreatitis appears to be an established yet rare safety concern with these agents.[63] Patients should be informed of the risk and appropriate monitoring should occur if a patient develops signs or symptoms of pancreatitis while taking a DPP-4 inhibitor.

DPP-4 plays an important role in T-cell activation. Theoretically, the inhibition of DPP-4 could be associated with adverse immunologic reactions. To date, however, there has been no evidence of clinically relevant changes in immune function.

There is no need to titrate the dose of DPP-4 inhibitors; however, dose adjustments for kidney function are required for alogliptin, saxagliptin, or sitagliptin (Table 94-8).

Thiazolidinediones

Pioglitazone and rosiglitazone are the two currently FDA-approved TZDs for the treatment of type 2 DM. They are oral agents, dosed once daily (Table 94-8). TZDs work by binding to the peroxisome proliferator activator receptor-γ (PPAR-γ), a nuclear receptor that is predominantly located on fat cells and vascular cells. Activation of PPAR-γ alters the transcription of several genes involved in glucose and lipid metabolism and energy balance. TZDs enhance insulin sensitivity at muscle, liver, and fat tissues. TZDs cause preadipocytes to differentiate into mature fat cells in subcutaneous fat stores. Small fat cells are more sensitive to insulin and more able to store FFAs. This allows a flux of FFAs out of the plasma, visceral fat, and liver into subcutaneous fat, a less insulin-resistant storage tissue. Muscle intracellular fat products, which contribute to insulin resistance, also decline. TZDs also affect adipokines (eg, angiotensinogen, tissue necrosis factor-α, interleukin 6, PAI-1), which can positively affect insulin sensitivity, endothelial function, and inflammation. Of particular note, adiponectin is reduced with obesity and diabetes, but is increased with TZD therapy, which improves endothelial function, insulin sensitivity, and has a potent anti-inflammatory effect.[64]

TZDs are considered second- or third-line agents and can be used in combination with metformin and other commonly prescribed medications for

type 2 DM. TZDs have high glycemic-lowering efficacy and reduce A1C values approximately 1.0% to 1.5% (0.010-0.015; 11-22 mmol/mol), FPG levels by 60 to 70 mg/dL (3.3-3.9 mmol/L) at maximal doses, and they have high durability over time. Glycemic-lowering onset is slow and maximal effects may not be seen until 3 to 4 months of therapy. It is important to inform patients of this fact and that they should not stop therapy even if minimal changes in BG levels are initially seen. Pioglitazone consistently decreases plasma triglyceride levels by 10% to 20%, whereas rosiglitazone tends to have a neutral effect. LDL-C concentrations tend to increase with rosiglitazone 5% to 15%, but do not significantly increase with pioglitazone. Both appear to convert small, dense LDL particles, which have been shown to be more atherogenic, to large, buoyant LDL particles, which may be less atherogenic. Both drugs increase HDL, though pioglitazone may raise it more than rosiglitazone. The ADA algorithm recommends TZDs as a potential second-line treatment choice for type 2 DM, particularly when medication cost is a major concern or for those with a compelling need to avoid hypoglycemia. They can be used in combination with metformin and other second-line options.[32,33]

The effects of TZDs on macrovascular complications are controversial and are not similar between rosiglitazone and pioglitazone. A meta-analysis published in 2007 reported higher rates of myocardial infarction (MI) with rosiglitazone compared to placebo or other diabetes medications.[65] This prompted a safety communication from the FDA and prescribing restrictions for the drug. These restrictions were later removed after re-evaluation of the data determined no increased risk. The prospective, multicenter, open-label trial found that rosiglitazone was noninferior to the metformin/sulfonylurea comparator for all CV outcomes except heart failure.[66,67] Alternatively, pioglitazone has been associated with benefits related to macrovascular outcomes. In the PROactive study, 3 years of pioglitazone 45 mg resulted in a significant reduction of the composite of all-cause mortality, nonfatal MI, or stroke in patients with type 2 DM who had previous macrovascular events.[68] Pioglitazone has also been shown to decrease the risk of recurrent strokes, but this was not in a diabetes population.

Adverse effects of TZDs include edema, new-onset or worsening of preexisting heart failure, weight gain, and bone fractures. TZDs cause fluid retention due to peripheral vasodilation and improved insulin sensitization at the kidney with a resultant increase in renal sodium and water retention. Resultant effects include peripheral edema, heart failure, hemodilution of hemoglobin and hematocrit, and weight gain. Peripheral edema is reported in 4% to 5% of patients using TZD monotherapy, but the incidence is significantly increased (more than 15%) when a TZD is used in combination with insulin. TZDs are contraindicated in patients with New York Heart Association Class III and IV heart failure, and great caution should be used in patients with Class I and II heart failure. Edema is dose-related and if not severe, a reduction in the dose may allow the continuation of therapy in the majority of patients. Rarely, TZDs have been reported to worsen macular edema of the eye. Weight gain is also dose-related and is a result of both fluid retention and fat accumulation. Average weight gain varies but a 4-kg weight gain is not uncommon; higher amounts of weight gain may necessitate discontinuation of therapy.

TZDs have also been associated with an increased fracture rate in the upper and lower limbs of postmenopausal women. The risk may relate to TZDs' effect on the pluripotent stem cell and shunting of new cells to fat instead of osteocytes as well as altering osteoblasts/osteoclasts.[69,70] A patient's risk factors for fractures should be considered before selecting a TZD.

TZDs have also been linked to bladder cancer. Bladder tumors have been noted in rodent models using TZDs. Interim analysis of a 10-year observational study with pioglitazone reported an excess of three cases of bladder cancer per 10,000 patient-years of treatment after 5 years of pioglitazone use. Ten-year data using the same database showed no association.[71,72] Other population-based and prospective studies have also reported increased risk with pioglitazone. Excess risk, if present, appears to be mostly in men and smokers, and is dose and duration associated. TZDs should not be used in patients with active bladder cancer and the benefits and risks should be carefully considered before using pioglitazone in patients with a history of bladder cancer.

Premenopausal anovulatory patients may resume ovulation on TZDs due to their insulin-sensitizing effects. Adequate pregnancy and contraception precautions should be explained to all women capable of becoming pregnant.

The recommended starting dosage of pioglitazone is 15 mg once daily and rosiglitazone is 2 mg once daily. Dosages may be increased after 3 to 4 months based on the response to treatment and side effects. The maximum dose and maximum effective dose of pioglitazone is 45 mg and 8 mg once daily for rosiglitazone (Table 94-8). To minimize weight gain and edema, the lowest effective dose should be used. If side effects occur with a higher dose, the dose should be reduced. Lower doses are recommended when used in combination with insulin, and edema and weight gain should be monitored carefully.

Sulfonylureas

Sulfonylureas are oral agents, available in either immediate-release or extended-release formulations, typically dosed once or twice daily (Table 94-8). They enhance insulin secretion by binding to a specific sulfonylurea receptor (SUR1) on pancreatic β-cells. Binding closes an adenosine triphosphate-dependent K^+ channel, leading to decreased potassium efflux and subsequent depolarization of the membrane. Voltage-dependent Ca^{+2} channels open and allow an inward flux of Ca^{+2}. Increases in intracellular Ca^{+2} bind to calmodulin on insulin secretory granules, causing translocation of secretory granules of insulin to the cell surface and resultant exocytosis of the granule of insulin. Elevated secretion of insulin from the pancreas travels via the portal vein and subsequently suppresses hepatic glucose production.

Sulfonylureas are classified as first-generation and second-generation agents. The classification schemes are based on relative potency. First-generation agents (chlorpropamide, tolazamide, and tolbutamide) are lower in potency relative to the second-generation drugs (glyburide, glipizide, and glimepiride), and are rarely used due to a higher risk of adverse effects. When given in equipotent doses, all sulfonylureas are equally effective at lowering BG. On average, glucose-lowering efficacy is considered high with A1C reductions of 1.5% to 2% (0.015 and 0.02; 16 and 22 mmol/mol) and FPG reductions of 60 to 70 mg/dL (3.3-3.9 mmol/L) in drug-naïve patients but is dependent on baseline values and duration of diabetes.

Sulfonylureas are the second most prescribed oral drugs for the treatment of type 2 DM. However, their place in therapy is controversial. Based on their extensive track record of safety and effectiveness, their low cost, and their oral route of administration, many clinicians feel comfortable using them. However, many diabetes experts as well as major organizations that publish guidelines for diabetes management either discourage the use of sulfonylureas or suggest using caution due to the risk of hypoglycemia and weight gain. Soon after sulfonylureas are taken, a robust reduction in A1C is seen, but long-term durability is poor in most patients. Sulfonylureas cause a tachyphylaxis to their insulin secretion effect on the β-cell. In vitro testing of β-cells has reported depolarization of the cell, resulting in its inability to secrete insulin. Whether this effect is reversible is unclear. Clinically, this is recognized by the deterioration of A1C.

Sulfonylureas were used extensively in the UKPDS and ADVANCE trials, which both showed a reduction in microvascular complications in patients targeting a more intensive glycemic goal.[20,24] Results from the University Group Diabetes Program raised early concerns about the CV safety of sulfonylureas, with documented higher rates of coronary artery disease in type 2 DM patients given tolbutamide compared to patients given insulin or placebo. Since then, most evidence suggests that sulfonylurea use does not increase macrovascular outcomes or all-cause mortality compared to other active treatments.[20,24,73,74]

The most common side effect of sulfonylureas is hypoglycemia. Due to its active metabolite, glyburide has a higher risk of hypoglycemia compared to other sulfonylureas while glipizide and glimepiride have lower risks.[74,75] Those who skip meals, exercise vigorously, or lose substantial amounts of weight are more prone to experiencing hypoglycemia. A lower dose should initially be used in high-risk patients, in addition, hypoglycemia on low-dose sulfonylureas may dictate a switch to therapy with a low risk of hypoglycemia. Severe hypoglycemia on sulfonylureas would warrant the same intervention. Because of their risk of hypoglycemia, sulfonylureas should be avoided or used with extreme caution in older adults.[28]

Weight gain is common with sulfonylureas—typically 1 to 2 kg. Whenever possible, clinicians should avoid the use of medications that cause weight gain in patients who are overweight or obese.[76] Many patients report having a sulfa allergy, but cross-reactivity with sulfonylureas is very rare. However, if the patient has a history of anaphylaxis-type reactions to sulfa, it may be best to use a different class of medication.

The starting dose, usual dose, and maximum dose of sulfonylureas are summarized in Table 94-8. Sulfonylureas with long durations of action or those with active metabolites should be avoided in older patients and those with kidney insufficiency due to the high risk of hypoglycemia, an alternative agent should be selected. Within the sulfonylurea class, glipizide may be the safest alternative. The dosage can be titrated as soon as every 2 weeks based on FPG values to achieve glycemic goals. Immediate-release glipizide's maximal dose is 40 mg/day, but its maximally effective dose is about 15 to 20 mg/day. Indeed, the maximally effective dose of sulfonylureas is typically 60% to 75% of the stated maximum dose.[32,77]

α-Glucosidase Inhibitors

Currently, there are two α-glucosidase inhibitors approved by the FDA, acarbose and miglitol, both of which are taken by mouth before meals. α-Glucosidase inhibitors competitively inhibit maltase, isomaltase, sucrase, and glucoamylase in the small intestine, delaying the breakdown of sucrose and complex carbohydrates. There is no malabsorption of these nutrients but merely a delay in their absorption. The net effect of this action is to reduce the PPG rise. Distal intestinal degradation of undigested carbohydrates by the gut flora results in gas, CO_2, and methane, as well as the production of short-chain fatty acids, which may stimulate GLP-1 release from intestinal L-cells.

The A1C-lowering effects of the α-glucosidase inhibitors are modest. PPG concentrations are reduced by 40 to 50 mg/dL (2.2-2.8 mmol/L) while FPG levels are relatively unchanged. Patients near target A1C with near-normal FPG levels but high PPG levels are candidates for therapy. Due to their mechanism, GI side effects, including flatulence, abdominal pain, and diarrhea, are very common and limit their use. Because of the modest A1C effect and the high rates of unpleasant side effects, the ADA does not include the class on their treatment algorithm, but the AACE/ACE algorithm considers them an alternative option that can be used when other medications may be contraindicated or the patient has intolerances. To effectively lower PPG, α-glucosidase inhibitors must be taken three times a day with the first bite of each meal.

Meglitinides

Meglitinides are similar to sulfonylureas, except they have a faster onset and shorter duration of action. By binding to a site adjacent to the sulfonylurea receptor, nateglinide and repaglinide stimulate insulin secretion from the β-cells of the pancreas. As monotherapy, both nateglinide and repaglinide significantly reduce PPG excursions and reduce A1C by approximately 0.8% to 1% (0.008-0.01; 9-11 mmol/mol). Similar to sulfonylureas, the main side effects are hypoglycemia and weight gain. Due to the lack of clinical evidence, their role in therapy is unclear. They are not recommended in the ADA algorithm and are considered a less favorable choice on the AACE/ACE treatment algorithm. Nateglinide or repaglinide should be taken by mouth with each meal, initiated at a low dose, and titrated over time until glycemic control is achieved. These agents may be used in patients with kidney insufficiency and may be a good option for those with erratic meal schedules. Multiple daily dosing may decrease adherence.

Bile Acid Sequestrants

The only bile acid sequestrant approved for the treatment of type 2 DM is colesevelam, an oral once-daily medication. Colesevelam acts in the intestinal lumen to bind bile acid, decreasing the bile acid pool for reabsorption. The role of bile acid sequestrants in the treatment of type 2 DM is unclear. A1C-lowering efficacy is modest. Colesevelam reduces LDL-C cholesterol in patients with type 2 DM by 12% to 16%. Colesevelam is weight neutral and has a low risk of hypoglycemia. Although colesevelam lowers plasma glucose and LDL-C, it has not been proven to prevent CV morbidity or mortality. Patients with type 2 DM who need a small reduction in A1C as well as additional LDL-C lowering may be candidates for this agent.

Dopamine Agonists

While bromocriptine has been used to treat Parkinson's disease and other disorders for decades, a new formulation, bromocriptine mesylate, was FDA-approved for the treatment of type 2 DM. Bromocriptine used for type 2 DM is a quick-release formulation of the dopamine agonist. The exact mechanism by which it improves glycemic control is unknown. Low hypothalamic dopamine levels, especially upon waking are augmented, which may decrease sympathetic tone and output. These effects are speculated to improve hepatic insulin sensitivity and decrease hepatic glucose output. The A1C-lowering efficacy is modest and its role in the treatment of type 2 DM is unclear.

Amylin Analogs

Pramlintide is a synthetic analog of amylin, differing from amylin by three amino acids. It is given subcutaneously before meals and is used in patients currently treated with insulin. Pramlintide mimics the action of amylin, a neurohormone co-secreted from the β-cells with insulin, and regulates glucose by three key mechanisms: reduces glucagon secretion, slows gastric emptying, and increases satiety.

Pramlintide was the first noninsulin agent approved for patients with type 1 DM. Pramlintide is effective at lowering PPG levels and A1C and can be an attractive option for some patients as it can also decrease weight and may allow for lower mealtime insulin doses. Pramlintide lowers A1C by approximately 0.6% (0.006; 7 mmol/mol) and produces an average weight loss of 1.5 kg in patients with type 2 DM. In patients with type 1 DM, the average reduction in A1C was 0.4% to 0.5% (0.004-0.005; 5-6 mmol/mol). Pramlintide is primarily used in patients with type 1 DM as adjunctive therapy in patients who are not achieving PPG goals despite maximizing mealtime insulin doses.

The most common adverse effects associated with pramlintide are GI. Nausea occurs in approximately 20% of patients with type 2 DM and 40% to 50% of patients with type 1 DM. Vomiting or anorexia occurs in approximately 10% of patients. GI adverse effects decrease over time and are dose-related, thus starting with a low dose and slowly titrating as tolerated is recommended. Pramlintide alone does not cause hypoglycemia, but when used in patients on insulin hypoglycemia can occur. To minimize the risk of severe hypoglycemia, the dose of mealtime insulin should be empirically reduced by 30% to 50% when pramlintide is initiated.

Pramlintide dosing is different in patients with type 1 DM and type 2 DM. In type 2 DM, the starting dose is 60 mcg prior to meals and is titrated to the maximally recommended 120-mcg dose as tolerated and warranted based on PPG concentrations. In type 1 DM, dosing starts at 15 mcg prior to meals and can be titrated up in 15-mcg increments to a maximum of 60 mcg prior to each meal, if tolerated.

Treatment—Type 2 Diabetes

Hyperglycemia management in patients with type 2 DM should be patient-centered, using shared decision-making and a stepwise approach.[12] The treatment approach should emphasize compelling evidence, avoiding adverse effects, minimizing hypoglycemia and weight gain, and be informed by financial considerations. Management decisions should focus on the impact on comorbidities in addition to the impact on glycemia. Upon diagnosis of type 2 DM, the clinician should assess key patient characteristics including current lifestyle, existing comorbidities, clinical characteristics including A1C, age, weight, presence or absence of symptoms, as well as motivation, cultural preferences, health literacy level, and cost limitations. A patient-specific A1C and other treatment targets should be set and discussed with the patient. Care systems should facilitate both in-person and virtual visits.

Initial Therapy

Comprehensive lifestyle modifications (medical nutrition therapy [MNT], physical activity, weight loss, smoking cessation, and psychological support) should be implemented at the time of diagnosis and reinforced at every visit since they are the foundational components of diabetes management. To achieve lifestyle modification goals, all patients with type 2 DM should be offered access to ongoing DSME/S programs.

MNT should include improved diet quality and calorie restriction for weight loss or weight maintenance. There is no specific recommended ratio of macronutrients for type 2 DM. Instead, patients should focus on eating patterns that promote foods of demonstrated health benefits and minimize foods of demonstrated harm. All overweight or obese patients should be encouraged to participate in intensive lifestyle management programs to lose weight, with an initial weight loss goal of 5%. Increased physical activity should be encouraged in all patients with type 2 DM to improve glycemic control. Most adults should engage in at least 150 minutes of moderate or vigorous intensity aerobic physical activity spread over the week with no more than 2 consecutive days without activity.[29]

Patients with type 2 DM should consider the quantity, quality, and timing of carbohydrate intake in their diet as a strategy to minimize glucose excursions. Patients should increase carbohydrate intake from vegetables, fruits, legumes, whole grains, and dairy products and should decrease processed foods, refined carbohydrates (ie, foods made with white flour or sugar), or foods/drinks high in added sugar (eg, soda, candy).[29] Quantities of carbohydrates should be considered, although the scientific evidence for specific recommendations is lacking. Education materials often encourage patients to limit daily carbohydrate intake to no more than 60 to 75 g/meal for men or 45 to 60 g/meal for women, and 15 g for snacks. An easier strategy is to limit the grain/starch of the meal to one-quarter of a 9-in. (23 cm) plate. Carbohydrate intake should be spread out across all meals and snacks.

9 In addition to comprehensive lifestyle modification, a person-centered approach should guide the initial medication choice taking into consideration cardiovascular and kidney benefits, glucose-lowering efficacy, impact on weight, cost, and adverse effects. In many patients, metformin is a reasonable initial treatment option. If metformin is used, it should be started at a low dose and titrated to the maximum effective dose over time to improve tolerability.[32,33] Current ADA and EASD guidelines no longer recommend metformin as the preferred first-line agent for all patients with type 2 DM.[32,78] In patients with a compelling indication such as comorbid HF, established ASCVD, or CKD, either an SGTL2 inhibitor or GLP-1 RA would be a reasonable initial treatment choice, instead of metformin, and should be used regardless of baseline A1c. However, cost remains a major consideration in selecting the most appropriate treatment. In the absence of a compelling indication, the benefits of using these newer and more expensive medications over metformin as the initial treatment for type 2 DM does not appear to be cost-effective.[79]

If a patient's initial A1C is close to goal (eg, ≤7.5% [0.075; 58 mmol/mol]) and there are no compelling indications to use a medication, the patient and clinician may consider initial treatment with lifestyle alone.[32] Since the effectiveness of most oral medications rarely exceeds a 1.5% (0.015; 16 mmol/mol) reduction in A1C, the clinician may consider starting two medications (typically metformin plus a second agent) if a patient's initial A1C is more than 1.5% (0.015; 16 mmol/mol) higher than the target A1C.[33] In addition, there is data to support that initial combination therapy can reduce glucose faster and maintain glycemic control for longer compared to a stepwise approach.[33] Early introduction of basal insulin should be considered in patients with very high A1C levels (>10% [0.10; 86 mmol/mol), those with symptoms of hyperglycemia, or those with evidence of catabolism (eg,

weight loss).[33]

To avoid therapeutic inertia, treatment should be reassessed and modified regularly. Patients not meeting their goals should be seen at least every 3 months. Those that are meeting their goals should be seen at least every 6 months. At these points of reassessment, an A1C level should be drawn, medication adherence should be evaluated, and lifestyle recommendations should be reinforced. If glucose targets have not been met, additional therapy should be added.[32,33]

Stepwise Addition of Medications

10 Type 2 DM is a progressive disease, and the majority of patients will eventually require combination therapy. Intensification beyond metformin monotherapy requires careful consideration of patient- and drug-related factors when determining the best regimen for a given patient. Patient-specific factors to consider when selecting a medication include the individualized A1C target and the presence of specific comorbidities (eg, ASCVD, heart failure, CKD, obesity). Drug-specific factors to consider include glucose-lowering efficacy, impact on other comorbidities, impact on weight and hypoglycemia risk, side effect profile, ease of use, and cost (Table 94-11).[32,33] Some combinations are more likely to achieve and maintain good glycemic control. For example, metformin combined with the GLP-1 RA liraglutide was significantly more likely to achieve and maintain an A1c <7% than either the DPP-4 inhibitor sitagliptin or the sulfonylurea glimepiride added to metformin in the GRADE study.[80]

TABLE 94-11

Considerations When Selecting Pharmacotherapy for Type 2 Diabetes

Medication Class	Primary Physiologic Action	A1C Reduction Efficacy	Hypoglycemia Risk[a]	Effect on Weight	ASCVD Effects	Cost	Oral/SC	Adverse Effects and Safety
Metformin	↓ hepatic glucose production	High	No	Neutral	Potential benefit	Low	Oral	GI (diarrhea), B12 deficiency
SUs	↑ insulin secretion	High	Yes	Gain	Neutral	Low	Oral	Hypoglycemia, weight gain
TZDs	↑ insulin sensitivity	High	No	Gain	Potential benefit (pioglitazone)	Low	Oral	Edema, weight gain, risk of heart failure, bone fractures, bladder cancer
DPP-4 inhibitors	↑ insulin secretion (glucose dependent); ↓ glucagon secretion (glucose dependent)	Intermediate	No	Neutral	Neutral	High	Oral	Risk of heart failure, pancreatitis, joint pain
SGLT-2 inhibitors	Blocks glucose reabsorption by the kidney, increasing glucosuria	Intermediate	No	Loss	Benefit[b] (empagliflozin, canagliflozin)	High	Oral	GU infections, risk of volume depletion, hypotension, risk of amputations, bone fractures (canagliflozin), risk of DKA
GLP-1 RAs GLP-1/GIP RAs	↑ insulin secretion (glucose dependent); ↓ glucagon secretion (glucose dependent); slows gastric emptying; ↑ satiety	High	No	Loss	Benefit (liraglutide, semaglutide, dulaglutide)	High	SC/Oral	GI (nausea, vomiting), injection site reactions, risk of thyroid C-cell tumors, pancreatitis, cholelithiasis
Basal insulin	↑ glucose disposal; ↓ hepatic glucose production; suppresses ketogenesis	High	Yes	Gain	Neutral	High	SC	Hypoglycemia, weight gain, injection site reactions

ASCVD, atherosclerotic CV disease; DKA, diabetic ketoacidosis; DKD, diabetic kidney disease; DPP, dipeptidyl peptidase; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide; GU, genitourinary; RA, receptor agonist; SC, subcutaneous; SGLT, sodium-glucose co-transporter; SU, sulfonylurea; TZD, thiazolidinedione.

[a]When used as monotherapy.

[b]Specific drugs listed as beneficial are based on current available evidence. It is not clear whether the benefit is a class effect.

The first consideration is whether the patient has indicators of high risk or established ASCVD, CKD, or HF. Because of evidence from CV outcome trials,

SGLT-2 inhibitors or GLP-1 RAs with proven CV benefit (canagliflozin, empagliflozin, dulaglutide, liraglutide, or SC semaglutide) are recommended as compelling agents to reduce the risk of major adverse CV events in patients with high risk or established ASCVD. If HF coexists, SGLT-2 inhibitors with a proven benefit of reducing HF progression (empagliflozin, canagliflozin, dapagliflozin) are recommended. In patients with CKD, SGLT-2 inhibitors documented to slow CKD progression (canagliflozin, dapagliflozin) are preferably recommended. If an SGLT-2 inhibitor is contraindicated or not tolerated, a GLP-1 RA with proven CVD benefit is recommended.[32] TZDs should be avoided in patients with HF. If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug, then triple therapy is warranted and a drug from the other class can then be added.[32] These recommendations are independent of baseline A1C, individualized A1C target, or metformin use. In other words, one of these medications should be added irrespective of the need for glucose control and this recommendation is actionable whenever these comorbidities become new clinical considerations regardless of background glucose-lowering medications.

In those without established ASCVD, CKD, or HF, other considerations should be taken into account. If there is a compelling need to promote weight loss, GLP-1 RAs are preferred but the SGLT2 inhibitors also have a favorable impact on weight. GLP-1 RAs have demonstrated varying amounts of weight loss in clinical studies, with the greatest weight loss seen with tirzepatide followed by semaglutide, liraglutide, and dulaglutide. If dual therapy does not achieve glycemic control, a drug from the other class can be added. If a GLP-1 RA or an SGLT-2 inhibitor cannot be used, a weight-neutral medication such as a DPP-4 inhibitor can be selected. Sulfonylureas, insulin, and TZDs are not preferred and should be used cautiously due to weight gain. If there is a compelling need to minimize hypoglycemia, DPP-4 inhibitors, GLP-1 RAs, SGLT-2 inhibitors, or TZDs could be added to metformin. DPP-4 inhibitors and GLP-1 RAs should not be used together due to similar physiologic actions. Basal insulin and sulfonylureas are not preferred in this setting as they increase the risk of hypoglycemia and should be considered only if necessary and used with caution. If there is a compelling need to minimize cost, sulfonylureas or TZDs can be considered.[33]

Addition of Injectable Medications

The approach to insulin use in type 2 DM is quite different than in type 1 DM. People with type 1 DM initiate intensive insulin regimens shortly after diagnosis and require basal and prandial insulin to achieve glycemic control. Some people with type 2 DM can be managed with oral medications for years before the addition of an injectable is needed. Insulin is recommended for patients with extreme (A1C >10% [0.10; 86 mmol/mol]) or symptomatic hyperglycemia. Otherwise, GLP-1 RAs are preferred over insulin as the first injectable agent. GLP-1 RAs have demonstrated equal or superior A1C-lowering efficacy compared to basal insulin and lead to weight loss instead of weight gain with a low risk of hypoglycemia. Most GLP-1 RAs are started at a low dose and titrated slowly to improve tolerability. If additional glucose-lowering is needed after the GLP-1 RA dose has been maximized, basal insulin can be initiated. Switching to a fixed-ratio combination of GLP-1 RA plus basal insulin could be considered as well. Basal insulin is started at a low dose (10 units once daily or 0.1-0.2 units/kg/day) and titrated slowly over time to a target FPG range. Many titration strategies are used in clinical practice. A common method is the 3-0-3 method where the patient checks FPG levels daily for 3 days and calculates the average of those three readings. If the average is greater than 130 mg/dL (7.2 mmol/L), then the patient increases the dose by 3 units. The patient continues this titration until achieving target FPG levels (ie, 80-130 mg/dL [4.4-7.2 mmol/L] for patients targeting an A1C <7% [0.07; 53 mmol/mol]) or until they have reached a basal insulin dose of 0.7-1.0 units/kg/day. If unexplained hypoglycemia occurs, the dose is decreased by 3 units. If the A1C target is not reached by maximally titrating basal insulin, it indicates that PPG levels are likely elevated. Thus, at that point, a medication that lowers PPG can be considered. GLP-1 RAs or SGLT-2 inhibitors should be considered if the patient is not already taking one. Prandial insulin is also an option.

A stepwise approach is recommended when initiating prandial insulin; starting with 4 units or 10% of the basal dose with the largest meal of the day. If the A1C is <8% (0.08; 64 mmol/mol), the basal dose can be decreased by the same amount to avoid hypoglycemia. The dose should be titrated over time to achieve target PPG levels <180 mg/dL (10.0 mmol/L). A second or third injection can be added to the other meals if needed. The addition of prandial insulin requires more BGM and patient knowledge and awareness of the relationship between insulin and carbohydrates. It also increases the risk of hypoglycemia and weight gain.[32,33]

It is important to re-evaluate the appropriateness of oral medications when a patient starts injectable agents. GLP-1 RAs can be used in combination with all oral agents except DPP-4 inhibitors. When insulin is started, metformin should be continued. TZDs should be stopped or the dose should be reduced. Sulfonylureas should be stopped, especially if prandial insulin is initiated. SGLT-2 inhibitors can be continued, although the patient should be educated about the risk of DKA, and DPP-4 inhibitors can be continued.[33]

Guideline Recommendations

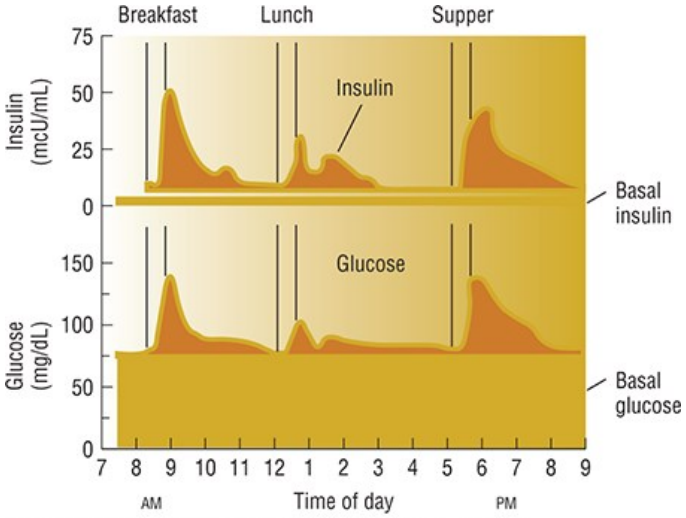
Several organizations, including the ADA and AACE, offer guidance for hyperglycemia management in patients with type 2 diabetes.[26,32,78] The ADA and AACE guidelines are similar, in that they both recommend a stepwise approach to treatment with lifestyle modifications. They also recommend the use of SGLT-2 inhibitors and some GLP-1 RAs in patients with established or high ASCVD risk, HF, and/or CKD, independent of glycemic control. The AACE guidelines recommend a more aggressive A1C target (<6.5% [0.065; 48 mmol/mol]) for most patients. Dual therapy is recommended initially for any patient with an A1C >7.5% (0.075; 58 mmol/mol) and insulin is recommended for patients with an A1C >9% (0.09; 75 mmol/mol) with symptoms. Finally, the AACE treatment algorithm lists drugs in order of preference with a focus on minimizing hypoglycemia, weight gain, and other adverse effects.[26]

Treatment—Type 1 Diabetes

11 Due to the absolute deficiency of endogenous insulin in people with type 1 DM, exogenous insulin therapy is a requirement. Achieving adequate glycemic control in type 1 DM usually requires intensive insulin therapy. Intensive insulin regimens are designed to provide insulin in a manner that mimics normal physiologic insulin secretion (Fig. 94-7), with the consistent secretion of basal insulin throughout the day to manage glucose levels overnight and in between meals (ie, basal insulin), and bursts of insulin in response to glucose rises after the ingestion of carbohydrates (ie, prandial insulin).

FIGURE 94-7

Relationship between insulin and glucose over the course of a day. Blood glucose values in mg/dL can be expressed in mmol/L by multiplying by 0.0555.



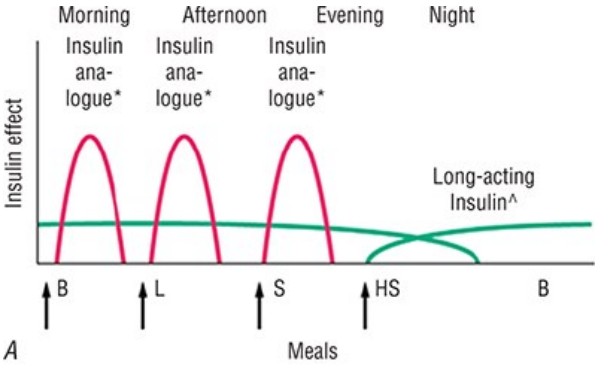
Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

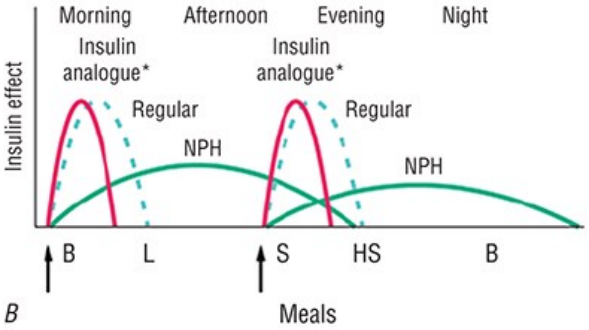
The ADA Standards of Care indicate that most people with type 1 DM should be treated with intensive insulin regimens, either multiple daily injections (MDI) or use of continuous subcutaneous insulin infusion (CSII) via an insulin pump.[32] The choice of which delivery method to use should be tailored to the individualized needs and preferences of the person with type 1 DM. Intensive insulin therapy is complex because it requires multiple injections or pump boluses per day in addition to basal insulin, routine monitoring, and collaborative decision making. The most successful therapy is delivered and adjusted based on changes in nutritional intake, glucose levels, stress, and physical activity.

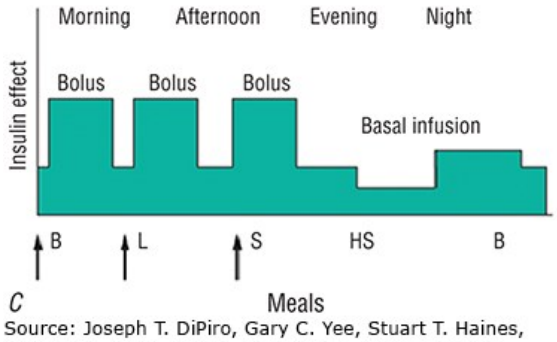
Examples of intensive insulin regimens are portrayed in Fig. 94-8. A common MDI approach is one injection of long-acting insulin (eg, insulin glargine U-100) to provide the basal component and three injections of rapid-acting insulin (eg, insulin lispro U-100) to provide the prandial component. This regimen utilizes insulin products with more ideal PK properties, but the cost can be prohibitive. A less expensive option consists of two injections of intermediate-acting insulin (eg, NPH insulin) and two injections of short-acting insulin (eg, regular insulin). However, the ADA Standards of Care recommend that most individuals with type 1 DM should use rapid-acting insulins as opposed to regular insulin to reduce the risk of hypoglycemia.[32]

FIGURE 94-8

Common insulin regimens. (A) Multiple-component insulin regimen consisting of one injection of long-acting insulin (^detemir, glargine, degludec) to provide basal glycemic coverage and three injections of rapid-acting insulin (*aspart, lispro, glulisine) to provide glycemic coverage for each meal. (B) Insulin regimen consisting of two injections of intermediate-acting insulin (NPH) and rapid-acting insulin (*aspart, lispro, glulisine [solid red line]), or short-acting regular insulin (green dashed line). Only one formulation of short-acting insulin is used. (C) Insulin administration by an insulin infusion device. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Rapid-acting insulin (aspart, lispro, or glulisine) is used in the insulin pump. *(Reproduced, with permission, from Lebovitz HE, ed. Therapy for Diabetes Mellitus and Related Disorders. 4th ed. Alexandria, VA: American Diabetes Association; 2004.)*







Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs. The pump infuses a basal rate constantly throughout the day and allows the patient to give bolus doses using a bolus dose calculator based on current glucose levels, carbohydrate intake, and insulin on board. Insulin pump therapy can provide more precise glucose control and allow more flexibility and fine-tune tailoring. However, CSII requires significant patient education and support and both MDI and CSII can achieve good glycemic control. Insulin pump technology is advancing quickly with new-generation devices entering the market regularly.

When initiating insulin therapy in someone with newly diagnosed type 1 DM, the starting dose is typically 0.4 to 1.0 units/kg/day of total insulin. The total daily dose of insulin is then divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals). As an example, an 80-kg patient initiated on 0.5 units/kg/day would start with a total daily dose of 40 units. He could be initially prescribed 20 units of a long-acting insulin such

as insulin detemir or glargine and 7 units of rapid-acting insulin, such as insulin aspart, lispro, or glulisine, with breakfast, lunch, and dinner. The insulin doses would then be adjusted based on BGM data.

The above example provides a starting point, but there is no one gold standard for starting insulin in patients with type 1 DM. Ideally, patients with type 1 DM should learn how to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake. Patients should also do BGM before each meal or use CGM to evaluate the insulin regimen and make treatment decisions. Bolus insulin doses can be better individualized by using carbohydrate to insulin ratios (C:I ratios) and correction factors (CF). The C:I ratio is used to estimate how many grams of carbohydrate each unit of rapid-acting insulin will cover. A typical C:I ratio for a patient with type 1 DM is 15:1, meaning that 1 unit of rapid-acting insulin will cover 15 g of ingested carbohydrates. An initial C:I ratio can be estimated by dividing 550 by the total daily dose of insulin the patient is taking. For example, if a patient was taking 40 units of insulin total per day, then his initial C:I ratio would be 550/40 = 14:1.

The CF is used to reduce high glucose levels detected before meals; it is the expected amount that one unit of insulin will decrease the BG under normal circumstances. The initial CF is estimated by dividing 1,650 by the total daily dose. For example, if a patient was taking 40 units of insulin per day, then his CF would be 1,650/40 = 41 (which would likely be rounded to 40 for easier use). Once the patient has a C:I and CF established, he can use these before each meal to calculate a specific premeal dose of rapid-acting insulin. For the example above, if the patient expected to eat 60 g of carbohydrates, had a premeal glucose reading of 200 mg/dL (11.1 mmol/L), and a target glucose of 100 mg/dL (5.6 mmol/L), he would take 7 units of rapid-acting insulin (60/14 = 4.3 units for the carbohydrates and 100/40 = 2.5 units for the correction).

The 550 rule and 1650 rule to calculate the C:I and CF are not well studied, and in clinical practice, some clinicians use 500 instead of 550 and others use 1,500 or 1,800 instead of 1,650. Regardless, these calculations provide an initial C:I and CF values that must be re-evaluated and adjusted over time based on glucose monitoring data.

Lifestyle modifications differ between type 1 DM and type 2 DM. Patients with type 2 DM are often encouraged to “count carbs” as a way to prevent glucose excursions after meals. This involves limiting carbohydrates to 45 to 75 g/meal or limiting starches/grains to one-quarter of a 9-in. (23 cm) plate. Patients with type 1 DM count carbs in order to match their prandial insulin dose with their carbohydrate intake using a C:I ratio. To be successful, this requires much more accurate estimations of carbohydrate content than what is needed for type 2 DM management.

Adjunctive Therapy

Pramlintide is an amylin agonist indicated as adjunctive treatment in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin. Pramlintide is discussed in more detail earlier in this chapter. In this setting, pramlintide may improve glycemic control and minimize weight gain caused by insulin. However, its use is limited by adverse effects such as nausea and vomiting, modest glucose improvements, increased injections and cost, and increased risk of hypoglycemia. Several other medications have been used off-label and/or are currently being studied as adjunctive therapy in type 1 DM, including the SGLT-2 inhibitors and GLP-1 RAs.

HYPOGLYCEMIA

Hypoglycemia is a common complication of some diabetes medications, including insulin, sulfonylureas, and meglitinides, and a major limiting factor to optimal glycemic control. Hypoglycemia can range in severity and is classified as level 1 (hypoglycemia alert value; ≤70 mg/dL [3.9 mmol/L]) which may not cause symptoms but is sufficiently low that it should be treated with a fast-acting carbohydrate; level 2 (clinically significant hypoglycemia; <54 mg/dL [3.0 mmol/L]) which is sufficiently low to indicate serious, clinically important hypoglycemia; and level 3 (severe hypoglycemia) which is associated with cognitive impairment requiring external assistance for recovery and can be life-threatening.[16] Hypoglycemia is associated with falls, injury, motor vehicle accidents, decreased quality of life, as well as an increased risk of CV events, QT prolongation, arrhythmias, and death. Recurrent hypoglycemia increases the risk of developing dementia, and the degree of cognitive impairment has been associated with the frequency and severity of hypoglycemia. All patients taking medications that can cause hypoglycemia should be educated about the prevention, detection, and treatment of hypoglycemia. BGM is essential to detecting hypoglycemia and taking appropriate action.

Patients can present with a variety of symptoms during an episode of hypoglycemia. Initial autonomic symptoms can include tachycardia, palpitations, sweating, tremors, and hunger. β-Blockers may mask some of these early symptoms. Neuroglycopenic symptoms often occur when the BG is <60 mg/dL (3.3 mmol/L) and can include cognitive impairment, confusion, behavioral changes, anger, irritability, blurred vision, headaches, seizures, and loss of consciousness. It is important for patients to self-monitor their BG when symptoms occur to confirm that the glucose is <70 mg/dL (3.9 mmol/L).

Some patients may experience hypoglycemia unawareness, defined as the asymptomatic onset of hypoglycemia. These patients are unable to detect the early warning symptoms of hypoglycemia and are thus at increased risk for the serious sequelae associated with severe hypoglycemia. Patients with hypoglycemia unawareness are typically those with longstanding disease, more stringent glycemic control, and frequent episodes of hypoglycemia. These patients should check their BG levels prior to any activities that require them to be alert and oriented (eg, driving). CGM can be particularly helpful to identify hypoglycemic events in patients with hypoglycemia unawareness. Also, temporarily raising glucose targets may reverse hypoglycemia unawareness.

Prevention of hypoglycemic events is a critical component of diabetes management. BGM can be helpful but may not be frequent enough to identify hypoglycemia. CGM can be particularly useful in preventing hypoglycemia since it provides the patient with glucose trends which patients can use to adjust their management decisions prior to becoming hypoglycemic. Patients must be educated to understand situations that increase their risk of hypoglycemia, including delaying meals, during or after exercising, or fasting for blood tests or procedures.

Treatment of hypoglycemia dictates the ingestion of carbohydrates. Glucose is preferred. Patients should be counseled to carry a source of fast-acting glucose with them at all times. The “rule of 15” is commonly used to teach patients the proper treatment. First, the patient should perform BGM to confirm a glucose <70 mg/dL (3.9 mmol/L) and then ingest 15 g of fast-acting carbohydrates (1/2 cup [125 mL] of milk, juice, or soda, one tablespoon of honey, hard candy, jelly beans, or glucose tablets or gel equivalent to 15 g of carbohydrates). Foods that include protein or fat should not be used acutely to treat hypoglycemia due to the delayed absorption of glucose. BGM should be repeated in 15 minutes; if the glucose remains <70 mg/dL (3.9 mmol/L), the process should be repeated. Once the BG is normalized, the patient should eat a snack or meal that includes complex carbohydrates and protein to prevent further hypoglycemic episodes.

If the patient is unconscious, IV glucose or glucagon (either via the intramuscular or intranasal route) should be given. Glucagon increases glycogenolysis in the liver and may be given in any situation in which IV glucose cannot be rapidly administered. A glucagon product should be prescribed and readily available to all patients on insulin who have a history of severe hypoglycemia or are at high risk for such events. Family and close friends of the patient should be educated regarding the preparation and administration of glucagon. It can take 10 to 15 minutes for the injection to start raising glucose levels and patients often vomit. It is important to position the patient on the side with the head tilted slightly downward to avoid aspiration. New glucagon products have been recently approved that make glucagon administration easier; a pre-filled syringe that is administered intramuscularly but does not require reconstitution and a dry powder nasal spray that is administered intranasally.

Finally, clinicians should inquire about hypoglycemia at every visit. This involves asking the patient about the frequency, severity, and timing of hypoglycemic events, the need for assistance by a third party, or the need to administer glucagon. Patients experiencing frequent or severe hypoglycemia should have their treatment regimen re-evaluated with a goal of minimizing hypoglycemia.

COMPLICATIONS AND COMORBIDITIES

Achieving good glycemic control is important to reduce the risk of both short-term and long-term complications in patients with type 1 or type 2 DM.[14] Short-term complications include symptoms of excessive urination, fatigue, and weight loss. In patients who are ketosis-prone, sustained elevations of BG above 200 to 300 mg/dL (11.1-16.7 mmol/L) can lead to DKA, a potentially life-threatening condition that often requires hospitalization to receive IV fluids and electrolytes. (See Chapter e95, “Acute Hyperglycemia.”) Even in patients who are not prone to ketosis, prolonged periods of poor glycemia can lead to HHS. Poor glycemic control can lead to an increased risk of soft-tissue and urinary tract infections, even in the short term. Long-term complications are the result of vascular and tissue damage. Long-term complications include ASCVD leading to CV events, nephropathy often resulting in kidney insufficiency, retinopathy potentially leading to vision loss, and neuropathy that can cause a wide variety of debilitating symptoms. The combination of vascular damage, peripheral nerve dysfunction, and a diminished immune response significantly increase the risk of toe, foot, and leg amputations in patients with diabetes. Males with diabetes are more prone to developing erectile dysfunction. In short, diabetes can negatively impact nearly every organ system throughout the body, and therefore a very comprehensive approach to patient monitoring is required.

Macrovascular Complications

12 Macrovascular complications are the leading cause of death in people with diabetes. The risk for coronary heart disease (CHD) and ischemic stroke is two to four times greater in patients with diabetes when compared to individuals without diabetes.[52] Moreover, CV disease is the leading cause of mortality in patients with DM. Addressing CV risk factors—dyslipidemia, hypertension, smoking cessation, and antiplatelet therapy—will reduce

macrovascular events. The ADA recommends low-dose aspirin therapy (75-162 mg daily) in all patients who have established ASCVD. If the patient is allergic to aspirin, clopidogrel may be used. The role of antiplatelet therapy for the primary prevention of a CV event in patients with diabetes is unclear. While low-dose aspirin reduces the risk of vascular events, in adults who do not have established ASCVD the benefits are offset by a higher risk of major bleeding.[81] Some clinical practice guidelines recommend aspirin therapy if the 10-year risk of a CV event is greater than 20% and the patient is at relatively low risk for bleeding complications. In patients who are older than 70 years of age, the risks outweigh the potential benefits of using antiplatelet therapy for the primary prevention of a CV event.

In patients with diabetes and established ASCVD, the use of a GLP-1 RA or an SGLT-2 inhibitor with a proven CV benefit should be strongly considered.[82] Several agents in these two classes of medications have been shown in clinical trials to reduce the risk of major cardiovascular adverse events in patients with a history of coronary artery disease, myocardial infarction, ischemic stroke, or peripheral artery disease and those at very high risk of vascular events with multiple ASCVD risk factors in addition to diabetes. The SGLT-2 inhibitors, specifically empagliflozin, canagliflozin, and dapagliflozin, significantly reduce the risk of hospitalization due to heart failure. Therefore, this class is preferred in patients with preexisting heart failure or those who are at high risk of developing heart failure due to structural heart disease.

Following a myocardial infarction, β-blocker therapy protects patients with diabetes from recurrent CHD events, and the magnitude of benefit is greater than that seen in patients without diabetes.[83] While the adrenergic symptoms produced by hypoglycemia (eg, tachycardia, tremor) can be masked by β-blockers, sweating and neuroglycopenic symptoms are not. Therefore, β-blockers should not be withheld in patients with diabetes if there is a compelling indication to use them.

13 High blood pressure increases the risk of both microvascular and macrovascular complications in patients with DM.[52] The ADA recommends dietary changes, specifically the Dietary Approaches to Stop Hypertension (DASH), and increased physical activity be instituted for all patients whose BP exceeds 120/80 mm Hg. Weight loss is also recommended in those patients who are overweight or obese. Pharmacological therapy, preferably using a class of agents proven to reduce CV event rates, should be instituted if the patient's confirmed office-based BP exceeds 130/90 mm Hg. A combination of two medications should be used if the blood pressure exceeds 160/100 mm Hg.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are often used as the initial pharmacological treatment for high blood pressure in patients with diabetes due to their well-documented CV and kidney protective effects.[52] However, thiazide diuretics and CCB have also been shown to improve outcomes in patients with diabetes. Most patients require multiple agents, on average three, to attain the BP goals. Thus, diuretics and calcium channel blockers frequently are used in combination with an ACE inhibitor or ARB. For more information regarding the treatment of hypertension in patients with diabetes, see Chapter 30, "Hypertension."

High-intensity statin therapy is recommended in all patients with diabetes and preexisting ASCVD.[52] For the secondary prevention of CV events, the goal of treatment is to achieve at least a 50% reduction in LDL cholesterol levels when compared to baseline and a target LDL-C < 55mg/dL. In patients who do not achieve the LDL-C target on a maximum tolerated statin dose, the addition of ezetimibe or a PCSK9 inhibitor is recommended. In the absence of ASCVD, a high-intensity statin to reduce LDL cholesterol by at 50% from baseline and to a target LDL-C less than 70mg/dL should be prescribed to all patients with type 1 or type 2 DM age 40 to 75. In patients younger than 40 years of age, moderate-intensity statin therapy may be appropriate if the patient has multiple CV risk factors.[84] The benefits of statins for the primary prevention of CV events in patients with diabetes were established in the Collaborative Atorvastatin Diabetes Study (CARDS).[85] Patients with diabetes and no documented ASCVD were randomized to atorvastatin 10 mg daily or placebo. The trial was stopped early because major CV events were reduced by 37% in the atorvastatin-treated patients. Data from the Heart Protection Study (HPS) also affirm the benefit of statin therapy. Simvastatin 40 mg daily reduced the risk of a major CV event in patients with diabetes by nearly 25% when compared to placebo-treated patients. Statin therapy is recommended regardless of baseline lipid or LDL-C levels. Because statins may cause birth defects, they should only be used in women of childbearing age who do not wish to become pregnant and are using a reliable form of contraception.

After a statin has been initiated for CV risk reduction, markedly elevated triglycerides (≥500 mg/dL [5.65 mmol/L]) may require additional therapy. Patients with marked hypertriglyceridemia are at risk for pancreatitis. In these circumstances, a fibrate (eg, fenofibrate), omega-3 fatty acid, or niacin can be used to reduce serum triglycerides.[86] The routine use of medications to address hypertriglyceridemia in patients with diabetes with baseline elevations less than 500 mg/dL (5.65 mmol/L) is controversial. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) was conducted in patients with type 2 DM and failed to show a CV benefit from fenofibrate 200 mg daily when compared to placebo. In a subgroup analysis, subjects without ASCVD at baseline appeared to have a significant reduction in CV events. However, the lipid arm of the ACCORD study also evaluated the use of

fenofibrate, and it did not significantly lower CV events. Niacin in combination with a statin failed to improve CV outcomes in patients with diabetes as well. For more information regarding the treatment of dyslipidemia in patients with diabetes, see Chapter 32, "Dyslipidema."

Peripheral arterial disease is another potential macrovascular complication associated with diabetes, which often contributes to foot ulcers and limb amputation.[52] Claudication and nonhealing foot ulcers are common in patients with type 2 DM. Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies in treating peripheral arterial disease. Cilostazol may be useful in select patients to reduce symptoms. Revascularization surgery can be considered; however, small vessel disease that cannot be bypassed is common in diabetes. If a patient develops foot lesions, early detection, debridement, and appropriate footwear are critical to prevent foot or limb loss. For more advanced lesions, skin grafts, topical wound healing, and hyperbaric treatments may be necessary. Foot examinations during each face-to-face encounter with the patient and a yearly Semmes-Weinstein 10 gram-force monofilament test to assess for loss of protective sensation can be used to identify high-risk patients who need further evaluation, routine podiatric care, and closer follow-up.

Microvascular Complications

Microvascular complications are closely related to glycemic control, and efforts to improve glycemia significantly reduce the risk of developing these complications and slow their progression.[87] Microvascular complications take many forms but most commonly manifest as damage to the kidneys, eyes, and peripheral nerves.

Nephropathy

DM, particularly type 2 DM, coupled with hypertension, are the leading causes of ESKD in the United States.[88] Albuminuria is a marker of kidney damage and a strong predictor of ESKD in patients with type 1 DM. In type 2 DM, the presence of albuminuria is a strong risk factor for macrovascular disease but a weaker predictor for ESKD. The ADA recommends measuring a patient's eGFR and screening for albuminuria at the time of diagnosis and annually thereafter in persons with type 2 DM. In type 1 DM, proteinuria rarely occurs before puberty. Annually screening individuals with type 1 DM should begin with puberty or when the disease duration has been at least 5 years. Patients with a UACR >300 mg/g or an eGFR 30-60 mL/min/1.73 m^2 should be monitored twice annually to guide therapy. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is the preferred method for determining eGFR. Race should no longer be used in the equation. There are three methods for assessing albuminuria: (1) a random spot collection, preferably the first-morning void; (2) a 24-hour timed collection; and (3) a timed (eg, 4- or 10-hour overnight) collection. Moderately elevated albuminuria is defined as a ratio of 30 to 299 mg/g (3.4-33.8 mg/mmol) albumin:creatinine and severely increased albuminuria as a ratio ≥300 mg/g (33.9 mg/mmol). Timed collections are cumbersome to perform but more accurate than a random spot collection. There is significant day-to-day variability in urinary protein excretion. Therefore, unless the results are unequivocally positive, albuminuria should be confirmed on at least two of three samples over 3 to 6 months. When assessing urine protein, conditions that may cause transient elevations in urinary protein or albumin excretion should be excluded. These conditions include intense exercise, recent urinary tract infections, hypertension, short-term hyperglycemia, heart failure, and acute febrile illness.

Achieving target blood pressure and glycemic goals are important for preventing and retarding the progression of nephropathy.[88] ACE inhibitors and ARBs have been shown to slow the progression of kidney disease in patients with diabetes. However, using a combination of agents to block the renin–angiotensin–aldosterone system—for example, using an ACE inhibitor with an ARB, mineralocorticoid receptor antagonist, or direct renin inhibitor—has not been shown to improve outcomes but clearly increase the risk of adverse effects. Diuretics frequently are necessary due to the volume-expanded state of patients with CKD and are recommended as second-line therapy. The ADA currently recommends a blood pressure goal less than 130/90 mm Hg, if it can be achieved without undue burden or side effects, may be desirable. Three or more antihypertensives are often needed to reach goal blood pressure.

The SGLT-2 inhibitors, specifically empagliflozin, canagliflozin, and dapagliflozin, significantly reduce the decline in kidney function in patients with CKD, with or without diabetes. Therefore, this class is preferred in the treatment of type 2 DM in patients with CKD, specifically in those with eGFR ≥20 mL/min/1.73 m^2 and a UACR >200 mg/g (22.6 mg/mmol). While the glucose-lowering effects of the SGLT-2 inhibitors are substantially reduced when the patient's eGFR is <45 mL/min/1.73 m^2, the kidney protective effects are not. The GLP-1 RAs also appear to slow the progression of CKD, but these findings have not yet been confirmed in studies specifically designed to determine the impact of GLP-1 RAs on kidney function in patients with CKD. Finally, in people with CKD and moderately to severely elevated albuminuria, the nonsteroidal mineralocorticoid receptor antagonist finerenone can be added and is recommended because it slows the progression of CKD and reduces the risk of CV events.

Retinopathy

Diabetic retinopathy is caused by ischemia in the microcirculation in the eye coupled with the inappropriate release of vascular growth factors.[87] Patients with diabetes should have routine dilated eye examinations to fully evaluate the retina. The ADA recommends patients with type 1 DM and patients with established retinopathy be seen by an ophthalmologist or optometrist trained in diabetic eye disease. Early background retinopathy may reverse with improved glycemic control and optimal blood pressure control. More advanced retinopathy will not fully regress with improved glycemia. Aggressive reductions in BG may acutely worsen retinopathy. Laser photocoagulation has markedly improved sight preservation and is recommended in patients with macular edema and proliferative retinopathy. Intravitreal anti-vascular endothelial growth factor (VEGF) therapy has also been shown to be highly effective for sight preservation. Both bevacizumab, used off-label, and ranibizumab are anti-VEGF monoclonal antibodies. Aflibercept is a VEGF decoy receptor. People with diabetes also have a higher rate of cataracts and open-angle glaucoma.

Neuropathy

Neuropathy in people with diabetes can manifest as (1) peripheral neuropathy, (2) autonomic neuropathy, and/or (3) focal neuropathies.[87] Distal, symmetrical, peripheral neuropathy is the most common complication seen in type 2 DM patients in outpatient clinics. Paresthesias, perceived hot or cold, numbness, or pain are the predominant symptoms. The feet are involved far more often than the hands as peripheral nerve damage initially affects longer nerve fibers and progresses proximally. Efforts to improve glycemic control are the primary treatment strategy and may alleviate some of the symptoms. If neuropathy is painful, symptomatic treatments can be used, but they will not change the course of the neuropathy. No medication has been shown to be clearly superior to another for the relief of neuropathic pain, and treatment selection should be based on adverse effects, cost, and convenience. Treatment with duloxetine, gabapentin, pregabalin, venlafaxine, low-dose tricyclic antidepressants (preferably nortriptyline or desipramine), topical capsaicin or lidocaine, or a sodium channel blocker (carbamazepine, oxcarbazepine, lamotrigine, or lacosamide) may be considered. If these are unsuccessful, patients should be referred to a pain clinic or neurologist for further evaluation. Duloxetine and pregabalin are FDA-approved for the treatment of neuropathic pain associated with diabetic peripheral neuropathy. For patients with numbness and minimal or no pain, medications are not effective. However, these patients are at high risk for developing foot ulcerations and should be carefully assessed at every face-to-face visit and preferably followed by a podiatrist.

Autonomic neuropathy impacts the autonomic nerves and can lead to resting tachycardia, orthostatic hypotension, chronic constipation, gastroparesis, erectile dysfunction, anhidrosis, heat intolerance, gustatory sweating, dry skin, and hypoglycemic unawareness.[89] Gastroparesis can be a severe and debilitating complication of DM. Improved glycemic control, discontinuation of medications that slow gastric motility, and the use of metoclopramide or low-dose erythromycin may be helpful. Unfortunately, tachyphylaxis to drug therapies develops within days or weeks. Gastric pacemakers can be considered if symptoms are severe and persistent. Domperidone may also be considered. Although it is not approved for use in the United States, domperidone is available in many other countries and can be requested through the FDA for compassionate use. Diabetic diarrhea most frequently occurs at night. Celiac disease, exocrine insufficiency, and gut bacterial overgrowth should be ruled out. Diabetic diarrhea frequently responds to a 10- to 14-day course of an antibiotic such as doxycycline or metronidazole. In more unresponsive cases, octreotide may be used.

If a patient develops orthostatic hypotension, antihypertensive agents should be discontinued, and dietary sodium intake should be liberalized. Some patients may require pharmacologic treatment for orthostatic hypotension with mineralocorticoids (eg, fludocortisone) or adrenergic agonist agents (eg, midodrine). In severe cases, supine hypertension may be extreme, mandating that the patient sleep in a sitting or semi-recumbent position. Patients with cardiac autonomic neuropathy are at a higher risk for silent MI and sudden cardiac death.

Erectile dysfunction is common in diabetes, and initial treatment should include a trial of one of the phosphodiesterase type 5 inhibitors (eg, sildenafil) prior to referral.[87] People with diabetes often require the highest doses of these medications to achieve an adequate response.

Sudomotor dysfunction may cause reduced sweating and dry, cracked skin. The use of hydrating creams and ointments is needed. Autonomic neuropathy may also result in gustatory sweating after eating. If sweating is excessive, it may be treated with antiperspirants or anticholinergic drugs. Hypoglycemic unawareness requires the patient to avoid hypoglycemia, as the body will slowly increase the glycemic level at which it will activate the autonomic signals.

Focal neuropathies occur most often in older patients with poorly controlled diabetes. Cranial nerve III, IV, and VI neuropathies, as well as Bell's palsy, produce quite dramatic symptoms, but the course is usually self-limited—partial or full recovery occurs in a few weeks to months. Diabetic

amyotrophy, which is characterized by proximal thigh muscle pain and weakness, can be very debilitating. Carpal tunnel syndrome, caused by radial nerve entrapment in the wrist, is also more common in people with diabetes, and tarsal tunnel syndrome may cause foot paresthesias.

SPECIAL POPULATIONS

Prediabetes and Preventing Type 2 DM

Prediabetes, as the name implies, is a condition that frequently precedes the development of diabetes.[4] Patients with prediabetes do not have marked elevated BG but rather IFG (100-125 mg/dL [5.6-6.9 mmol/L]) or IGT (140-199 mg/dL [7.8-11.0 mmol/L] 2 hours after ingesting a 75 g carbohydrate load) and often an elevated A1C (5.7%-6.4% [0.057-0.064; 39-46 mmol/mol]). None of these abnormal readings is sufficiently high to meet the diagnostic criteria for diabetes. One in three adults in the United States has prediabetes.[2] Most patients with prediabetes are overweight or obese, and many concurrently have high blood pressure and dyslipidemia. This is an important patient population to identify because they are at high risk of eventually developing type 2 DM.

14 Given that prediabetes often progresses, there has been significant interest in using both nonpharmacologic and pharmacologic means to prevent or delay the onset of type 2 DM. Weight loss, regular aerobic activity, increased fiber intake, and limiting fat consumption are the four lifestyle pillars for both the treatment and prevention of type 2 DM. The Diabetes Prevention Program (DPP) was a landmark clinical trial that demonstrated that modest weight loss and regular physical activity dramatically reduced the risk of developing type 2 DM in patients with IGT.[90] Patients assigned to the lifestyle intervention group walked 30 minutes per day 5 days per week and lost a mean of 8-lb (3.6 kg) over the 2.8-year study. These lifestyle changes resulted in a 58% reduction in the risk of developing type 2 DM when compared to a usual care group (5% per year vs 11% per year). Diet and exercise interventions were effective regardless of age or baseline weight. A third arm of the study randomized patients to receive metformin 850 mg twice daily. The patients in the metformin arm received usual care and did not engage in intensive lifestyle changes. Metformin use leads to, on average, a 4-lb (1.8 kg) weight loss and reduces the risk of developing type 2 DM by 31% when compared to usual care. Younger and overweight individuals who took metformin experienced the greatest reductions. These findings suggest that metformin use may have the greatest impact when prescribed to middle-aged adults who are obese.

Several other medications have also been shown to delay or prevent diabetes. Rosiglitazone and pioglitazone reduce the risk of developing type 2 DM by 60% to 70% in patients with impaired glucose tolerance.[91,92] Acarbose reduced the risk of developing type 2 DM by 25% in the STOP NIDDM study and may be particularly useful in patients who consume a diet high in starchy carbohydrates such as rice. The GLP1-RAs, liraglutide and semaglutide, have also been shown to slow the progression to type 2 DM, reducing the risk by 80% in obese patients taking the medication for weight loss.[93,94] Insulin glargine reduced the risk of developing type 2 DM by approximately 30% in patients with prediabetes. ACEi or ARBs have also been shown to lower the risk of developing type 2 DM by 25% in a pooled analysis of several large CV studies.[95] Given that many patients with prediabetes concurrently have high blood pressure, an ACEi or ARB should be preferentially used in this population to treat hypertension.

Unfortunately, pharmacological methods to “prevent” diabetes do not cure but rather delay the onset of diabetes. No pharmacologic agent is currently FDA-approved for the prevention of type 2 DM. Given its relatively low cost and favorable long-term safety profile, metformin, in conjunction with lifestyle changes, is recommended by the ADA to delay the onset of diabetes in patients with prediabetes, particularly those with a BMI >35 kg/m^2, those aged <60 years, and women with a history of GDM.[96] Liraglutide and once-weekly semaglutide are attractive options for weight loss in obese patients with prediabetes.

Children and Adolescents with Type 2 DM

The incidence and prevalence of type 2 DM are increasing in adolescence.[97] Obesity and physical inactivity are the likely culprits, but innate genetic susceptibility is also an underlying factor. Given that children will potentially live with diabetes for many decades and that the timeline for microvascular complications mimics that of adults with diabetes, extraordinary efforts should be made to assist the child and the family adopt lifestyle changes that normalize BG. The only FDA-approved oral agent for the treatment of type 2 DM in children (10-16 years of age) is metformin, and, similar to adult guidelines, some experts recommend its routine use in the absence of contraindications. Unfortunately, the durability of the response to metformin monotherapy is relatively poor. Liraglutide and exenatide XR have also recently been approved for use in children (10 years of age and older). Sulfonylureas are also commonly used. TZDs improve glycemic control when added to metformin therapy but are not currently FDA-approved

for use in children. While the DPP-4 inhibitors are an attractive option because they do not cause hypoglycemia, this class of medications has not been adequately studied in children. Insulin therapy continues to be the standard of care when glycemic goals cannot be achieved or maintained with metformin monotherapy. See Table 94-6 for treatment goals in children and adolescents.

Older Adults

Nearly one in four adults over the age of 65 years has diabetes, and slightly more than half have prediabetes. Older adults, particularly those with functional disability and cognitive impairments, are less able to adopt healthy lifestyle behaviors and more likely to experience adverse effects from medications.[28] The ADA guidelines recommend a patient-centered approach, and there are several factors that should be considered when treating older adults. The number and severity of comorbid conditions, kidney dysfunction, ability to engage in self-care, nutritional status, social support, the risk of falls, and life expectancy should all influence glycemic goals and treatment selection. (See Table 94-6 and Fig. 94-6.) The ADA recommends an A1C goal ≤7.0%-7.5% (0.070-0.075; 53-58 mmol/mol) for otherwise healthy older adults who have intact cognitive function, but a less stringent goal A1C ≤8.0% (0.080; 64 mmol/mol) is reasonable in those with multiple chronic diseases. In patients who have limited life expectancy, significant cognitive impairments, require long-term care, or are unable to engage in activities of daily living, an A1C should not be used as the primary means to guide therapy. Instead, clinicians should use blood glucose monitoring to keep fasting blood glucose between 100 and 180 mg/dL (5.6 and 10.0 mmol/L) to avoid hypoglycemia.

Older adults often have altered perceptions of hypoglycemia and may not experience adrenergic symptoms (eg, tremor, jitteriness, palpitations) due to the age-related loss of autonomic nerve function.[28] Thus, neuroglycopenic symptoms (eg, altered mental status, personality changes) may be the first indication the patient's BG is low. For these reasons, over-treatment of DM should be avoided, and de-escalation should be strongly considered should severe or frequent hypoglycemia occur. Older adults in long-term care facilities are particularly vulnerable to hypoglycemia. However, glycemic control should not be relaxed so far as to cause symptoms of hyperglycemia or risk the development of DKA or HHS.

Other therapeutic goals related to the management of blood pressure and dyslipidemia to prevent the development or progression of kidney disease and CV complications should be similarly tailored in older adults based on the patient-specific circumstances.[28] While a decline in kidney function may preclude the use of metformin in some older adults, lower doses may be used if coupled with more frequent monitoring (eg, every 3 months) of kidney function when the eGFR is consistently above 30 mL/min/1.73 m^2.[28] The efficacy of the SGLT-2 inhibitors declines as kidney function declines, thus older adults typically have a diminished glucose-loweringresponse to this class of agents. SGLT-2 inhibitors may also increase the frequency of urination and cause orthostatic blood pressure changes, increasing the risk of falls.

Sulfonylureas, particularly longer-acting agents such as glyburide and chlorpropamide, are more likely to cause hypoglycemia and should be avoided. A higher risk of distal extremity fracture from falls has been documented with canagliflozin as well as the TZDs. The TZDs often cause fluid retention and increase the risk of congestive heart failure. DPP-4 inhibitors are generally well-tolerated and do not cause hypoglycemia. Similarly, α-glucosidase inhibitors are generally safe and may also be used. The GLP-1 RAs and the SGLT-2 inhibitors are unlikely to cause hypoglycemia and produce a modest weight loss, which can be advantageous in overweight individuals. However, older patients may be more prone to GI side effects from GLP-1 RAs. Simple insulin regimens using a single daily basal insulin dose can be used in older adults, especially if tight glycemic control is not the goal. Both the injectable GLP-1 RAs and insulin therapy require the patient to have adequate motor skills and visual acuity to self-administer doses.

Pregnant Women

The prevalence of DM has increased significantly among women during their reproductive years.[13] In women with type 1 or type 2 DM, discussions about family planning and achieving good glycemic control prior to pregnancy are critical. Organogenesis is largely completed within the first 8 weeks of pregnancy—well before good glycemic control can be achieved in the absence of preconception planning. Unfortunately, major congenital malformations due to poor glucose control in the first trimester of pregnancy remain the leading cause of mortality and serious morbidity in infants of mothers with DM. During preconception planning, all drugs should be reviewed for safety. Known teratogens, such as ACE inhibitors and statins, should be stopped and, if treatment is still needed, an appropriate alternative recommended.

GDM is diagnosed during pregnancy, and all women should be screened for GDM between weeks 24 and 28 of the pregnancy. See Table 94-5. The adverse outcomes associated with GDM include birth defects, miscarriage, cesarean section delivery, maternal preeclampsia/eclampsia, preterm delivery, neonatal hypoglycemia, shoulder dystocia, birth injury, and hyperbilirubinemia.[13] Medical nutritional therapy to minimize wide fluctuations

in BG is of paramount importance. Intensive educational efforts are usually necessary. Pregnant women without DM maintain plasma glucose concentrations between 50 and 130 mg/dL (2.8 and 7.2 mmol/L). Normoglycemia is the goal, and failure to maintain this despite dietary interventions will necessitate medication use. Goals during therapy are to keep fasting glucose less than 95 mg/dL (5.3 mmol/L), and either a 1-hour postprandial plasma glucose levels less than 140 mg/dL (7.8 mmol/L) or 2-hour postprandial plasma glucose levels less than 120 mg/dL (6.7 mmol/L). See Table 94-6. Ketosis should also be avoided as much as possible.

Similarly, in patients who have preexisting type 1 or type 2 DM who become pregnant, premeal, bedtime, and overnight BGM should be less than 95 mg/dL (5.7 mmol/L) with a peak PPG less than 140 mg/dL (7.8 mmol/L). While the A1C during pregnancy should ideally be between 6% and 6.5% (0.06 and 0.065; 42 and 48 mmol/mol), BGM must be used to guide therapy because it provides daily information about glycemic control. In women with type 2 DM controlled by lifestyle modification alone, conversion to insulin is often necessary soon after the pregnancy is confirmed. Patients previously treated with insulin typically need to intensify the regimen to achieve the more stringent therapeutic goals recommended during pregnancy. This may require the use of more complicated regimens coupled with carbohydrate counting and adjustments guided by BGM. While NPH remains the recommended basal insulin to use during pregnancy, insulin detemir appears to be safe. Insulin pump therapy can be considered. In highly motivated patients, CSII can achieve excellent glycemic control and is routinely adjusted throughout the pregnancy.

In women with type 2 DM or GDM, both metformin and glyburide have been studied as alternatives to insulin therapy.[13] Both appear to be effective and safe based on the results of small randomized controlled trials and meta-analyses. However, rare or uncommon adverse fetal events are difficult to discern from these data. Glyburide was not detected in the cord serum of any infant in one study, whereas metformin crosses the placenta. Further study in larger patient populations is needed prior to routinely recommending them, but in patients for whom the complexity of insulin is too difficult or refuses insulin, glyburide or metformin use is justified. Patients with GDM should be evaluated approximately 6 weeks after delivery to ensure that normoglycemia has returned. The lifetime risk for the development of type 2 DM is 30% to 50%, making the periodic screening of women with a history of GDM warranted.

Patients with HIV

Patients living with HIV are at higher risk for developing type 2 DM. This risk may be related to HIV infection, concomitant infections such as hepatitis C, and medications often used to treat HIV and its comorbidities. Pentamidine, used for *Pneumocystis carinii* pneumonia infections, is a β-cell toxin and may cause some patients to develop hypoglycemia from insulin release followed by hyperglycemia. Megestrol, used as an appetite stimulant, can have glucocorticoid-like effects and cause hyperglycemia in some patients. Protease inhibitors, used to treat HIV infection, can worsen insulin sensitivity, decrease the ability of the β-cell to secrete insulin, and worsen lipotoxicity. Long-term use of stavudine also increases the risk of developing diabetes. Redistribution of fat from subcutaneous to the visceral compartment from medications or HIV infection also increases the risk of developing diabetes. Metformin is the drug of choice for HIV patients as weight gain can be minimized. Stavudine, zidovudine, and didanosine may cause lactatemia, especially upon long-term use. It may be advisable to check lactate levels in patients taking these medications prior to metformin use. If lactate levels are greater than two times normal, alternative therapy should be considered. If excess visceral adiposity is noted, a TZD that redistributes fat into subcutaneous adipose tissue and causes visceral fat apoptosis may be considered. Drugs that promote weight loss should also be considered. Significant drug-drug interactions may also be present.

EVALUATION OF PATIENT OUTCOMES

Glycemic control can be measured in several ways.[98] Plasma and BG measurements collected during fasting and postprandial periods can be used to determine the patient's current glycemic status. CGM devices collect glucose monitoring data throughout the day. These tests of glycemia are useful for detecting hypoglycemia, making adjustments in insulin therapy, and determining the patient's glycemic patterns. For those using a CGM, time in range (TIR), time below range, and glycemic variability are useful markers of glycemic control. The A1C is the gold standard for determining overall glycemic control for the previous 2 to 3 months and correlates with the risk of developing many of the long-term complications associated with diabetes. Fructosamine, which measures the amount of glycation on plasma proteins such as albumin, is a test of glycemia that can be useful in patients with altered red blood cell lifespan or a hemoglobinopathy. Fructosamine measures glucose control over the previous 2 to 3 weeks. Unfortunately, fructosamine is not as reliable as the A1C, and the correlation between fructosamine measurements and the risk of complications from diabetes is unknown. Thus, glycemic goals based on fructosamine have not been established.

While these glycemic goals recommended by the ADA and AACE are useful general targets, treatment goals need to be individualized. Less stringent

A1C goals are appropriate in patients with a history of severe hypoglycemia, limited life expectancy, advanced micro/macrovascular complications or comorbidities, and in patients who are frail, have dementia, or have limited social or financial resources. Less stringent goals should also be set for younger children. Conversely, more aggressive glycemic goals are appropriate in patients who are young or middle-aged adults, newly diagnosed, and using treatments that are unlikely to cause hypoglycemia.

BGM and CGM are important tools that provide an opportunity to adjust medications, food intake, or physical activity. BGM and CGM improve safety by enabling patients to detect hypoglycemia so that it can be treated. In general, BGM frequency should match how frequently medication changes are needed to achieve glycemic control as well as the risk of hypoglycemia. BGM and CGM empower patients to make day-to-day adjustments in prandial insulin doses and are used to determine if corrective doses of insulin are needed. Even in patients who do not use insulin therapy, BGM and CGM can be useful to see how a change in diet or exercise impacts BG. BGM readings are needed to check the accuracy of some CGM devices. For patients with type 1 DM, CGM is generally preferred, but BGM can be performed four to six times per day—prior to food intake and physical activity as well as at bedtime. The optimal frequency of BGM and the use of CGM in patients with type 2 DM on oral agents is unknown and its role controversial. BGM and CGM in patients with type 2 DM may be useful in patients who are actively using the information to make changes in their lifestyle behaviors and for a few weeks after medication changes.

The use of CGM has become increasingly common and helpful in patients using intensive insulin therapy. CGM measures interstitial glucose, which lags behind fingertip capillary BGM. CGM can be particularly useful in patients with frequent episodes of hypoglycemia, hypoglycemic unawareness, and nocturnal hypoglycemia. CGM can be used to identify glucose patterns and evaluate patients with higher or lower than expected A1C results. Some CGMs must be calibrated using BGM readings after insertion of a new sensor and periodically thereafter. A new sensor must be placed every 7 to 14 days. CGM data can be transmitted to insulin pumps which can then make recommendations to the patient or automatically adjust the insulin doses based on the results. The ADA currently recommends daily use of personal CGM in patients on intensive insulin therapy to lower or maintain A1C levels and/or reduce hypoglycemia.

Alternate site testing for BGM performed on the palm, forearm, or thigh is less painful than obtaining blood samples from fingertip samples, but only some BG test strips are designed for alternative site testing. Alternate sites tend to have fewer nerve endings than fingertips and may be more comfortable for a patient. Glucose readings obtained from alternative sites will lag behind fingertip capillary blood by 20 to 30 minutes. Therefore, alternate site testing is discouraged in any situation where immediate action will be needed based on the glucose reading, such as testing for hypoglycemia or when the BG is changing rapidly, such as after a meal.

Choosing an appropriate meter to perform BGM depends on the patient's dexterity, vision acuity, cost of the meter and strips, and desired features. Insurance coverage often influences meter choice. When a patient first obtains a new glucometer, it is important to demonstrate the testing methods and have the patient perform the technique. Each meter has specifications for hematocrit, elevation, and temperature tolerances for optimal operation.

Medication Adherence and Persistence

Despite the armamentarium of treatment options, a large percentage of patients fail to achieve target A1C and blood glucose levels. One major contributing factor to uncontrolled diabetes is poor medication adherence and persistence. Key contributors to adherence include perceived efficacy, hypoglycemia, weight gain, treatment complexity, convenience, cost, patient beliefs about medications, and trust in the healthcare provider.[99] Therefore, it is crucial to assess adherence and barriers to adherence at every visit and include the patient in the decision-making process. Simplifying the treatment regimen may improve adherence and glycemic control. Fixed-dose combination products may be one way to simplify treatment and have been shown to improve adherence and glycemic control.[100,101]

Therapeutic Inertia

15 Another contributing factor to uncontrolled diabetes is therapeutic inertia, which is the failure to initiate or intensify therapy in a timely manner according to evidence-based clinical guidelines. Several studies have shown that it often takes years before treatment is intensified in patients with uncontrolled diabetes. There are multiple reasons for therapeutic inertia including barriers at the patient, provider, and system level. Given the risk of development or progression of diabetes-related complications during treatment delays, it is vital that clinicians combat therapeutic inertia by routinely monitoring patients with DM and taking action in those who are not achieving therapeutic targets.[102]

CONCLUSION

DM is a heterogeneous group of metabolic disorders which all have elevated BG as their defining characteristic. Achieving good glycemic control, although important, is but one ingredient to optimal health outcomes in patients with diabetes. A comprehensive plan of care should include not only pharmacological and nonpharmacological strategies to lower BG but also methods to screen, prevent, and manage microvascular and macrovascular complications. Current Health Plan Employer Data and Information Set (HEDIS), performance measures annually reported by the National Committee for Quality Assurance (NCQA), recognizes that quality care to patients with diabetes must address glycemia, blood pressure control, statin use, and recommended screening exams.[12] Diabetes is a life-long disease, and patients with diabetes need ongoing support through an interprofessional, team-based approach to care. Adjustments to diet, exercise, and pharmacologic therapies are frequently needed. Clinical inertia should be avoided, and treatment intensification should be implemented if treatment goals have not been met. Patients should receive follow-up care every 3 months, but more frequent follow-up may be necessary if treatment changes have been made. The A1C should be measured every 3 to 6 months, even in patients who are stable on a therapeutic regimen and meeting treatment goals. Identifying and mitigating CV risks—particularly high blood pressure, dyslipidemia, and tobacco use—is critical. Blood pressure should be measured at every encounter and, in patients with elevated blood pressure, home blood pressure monitoring is strongly encouraged. A fasting lipid profile should be obtained as part of an initial assessment and to determine if statin therapy has adequately reduced LDL cholesterol. Performing foot examinations at each face-to-face visit and obtaining a dilated eye examination at least once a year are also important. People with diabetes should receive the influenza vaccine every year and the pneumococcal, zoster, and heptatitis vaccinations per Center for Disease Control and Prevention recommendations. Using an integrated electronic health record, standardized progress notes, and flow sheets can assist the clinician to determine whether the patient has met these standards of care. As with many chronic diseases, adherence to dietary recommendations, physical activity, and medications is a challenge for most patients. Frequent follow-up, patient education, and positive family engagement can help patients with diabetes lead healthier, happier lives.

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AADE	American Association of Diabetes Educators
ADA	American Diabetes Association
A1C	hemoglobin A1C
ASCVD	atherosclerotic cardiovascular disease
BG	blood glucose
BGM	blood glucose monitoring
BP	blood pressure
BMI	body mass index
CDCES	Certified Diabetes Care and Education Specialist
CF	correction factor
CGM	continuous glucose monitor
CHD	coronary heart disease

C:I	carbohydrate to insulin ratio
CKD	chronic kidney disease
CSII	continuous subcutaneous insulin infusion
CV	cardiovascular
CVD	cardiovascular disease
DKA	diabetic ketoacidosis
DPP-4	dipeptidyl peptidase-4
DM	diabetes mellitus
DSME/S	diabetes self-management education/support
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FDA	Food and Drug Administration
FFA	free fatty acid
FPG	fasting plasma glucose
GDM	gestational diabetes
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GLP-1/GIP RA	glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonist
GU	genitourinary
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HHS	hyperglycemic hyperosmolar syndrome
ICAs	islet cell autoantibodies
ICU	intensive care unit

IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IV	intravenous
LADA	latent autoimmune disease in adults
LDL-C	low-density lipoprotein cholesterol
MDI	multiple daily injections
MNT	medical nutrition therapy
MODY	mature-onset diabetes in the young
NPH	neutral protamine Hagedorn
OGTT	oral glucose tolerance test
PAI-1	plasminogen activator inhibitor-1
PK/PD	pharmacokinetic/pharmacodynamic
POC	point of care
PPAR-γ	peroxisome proliferator activator receptor-γ
PPG	postprandial glucose
SC	subcutaneous
SGLT-2	sodium-glucose co-transporter 2
SU	sulfonylurea
TZD	thiazolidinedione
UGE	urinary glucose excretion
VAT	visceral adipose tissue
XR	extended-release

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SELF-ASSESSMENT QUESTIONS

1. Which of the following best describes the biochemical derangements and clinical features associated with type 1 diabetes mellitus?

A. Hyperinsulinemia, ketosis-prone, patients usually present with hypoglycemia

B. Insulin resistance, loss of phase 1 insulin release, most commonly develops in older adults

C. Low C-peptide concentrations, beta cell destruction, most commonly develops in adolescents

D. High postprandial GLP-1 levels, obesity, patients usually present with no or only mild symptoms

2. All of the following are commonly observed in patients with type 2 diabetes mellitus EXCEPT:

A. Declining β-cell mass

B. Reduced hepatic glucose output

C. Increased postprandial glucagon release

D. Diminished incretin hormone release following meals

3. Which of the following would meet the diagnostic criteria for diabetes mellitus?

A. A fasting plasma glucose of 119 mg/dL (6.6 mmol/L)

B. A hemoglobin A1C value of 6.6% (0.066; 49 mmol/mol)

C. A plasma glucose of 181 mg/dL (10.0 mmol/L) at 2 hours during a 75-g oral glucose tolerance test (OGTT)

D. A random plasma glucose of 192 mg/dL (10.7 mmol/L) after a meal; the patient reports no symptoms and gained 5 lb (2.3 kg) over the last 6 months

4. A 20-year-old obese male is newly diagnosed with diabetes mellitus. His father (now age 53) was diagnosed with diabetes when he was 44 years old during a routine physical exam. His only sibling, his sister (now age 25) was diagnosed with impaired fasting glucose when she was 19 years old. His father achieved good glycemic control using two oral agents for several years but last year he required insulin therapy to achieve his glycemic goals. His sister began exercising and lost more than 40 lb (18 kg) after learning her blood glucose was abnormal. Her most recent fasting blood glucose reading was 93 mg/dL (5.2 mmol/L) and her A1C was 5.4% (0.054; 36 mmol/mol). What is the most likely etiology of their diabetes mellitus?

A. Type 1 DM

B. Type 2 DM

C. Mature-onset diabetes in the young (MODY)

D. Latent autoimmune diabetes in adults (LADA)

5. A patient with type 2 diabetes mellitus with insulin resistance is currently using a total daily dose of 320 units of insulin per day. The patient's last A1C measured this week was 7.8% (0.078; 62 mmol/mol). The patient is being transitioned to a concentrated insulin product. Which of the following would be the most appropriate treatment plan?

A. Switch to U-300 insulin glargine: inject 240 units subcutaneously daily (given as three injections of 80 units each once daily)

B. Switch to U-200 insulin lispro: inject 160 units subcutaneously twice daily (given as two injections of 80 units each twice daily)

C. Switch to U-200 insulin degludec: inject 180 units subcutaneously twice daily (given as two injections of 90 units each twice daily)

D. Switch to U-500 regular human insulin: inject 100 units subcutaneously three times daily before meals (given as one injection of 100 units each three times a day)

6. All of the following are potential effects associated with sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) use *EXCEPT*:

A. Heart failure

B. Weight loss

C. Dizziness/lightheadedness

D. Genitourinary infections

7. GLP-1 receptor agonists lower glucose levels by all of the following physiologic actions *EXCEPT*:

A. Increase glucose-dependent insulin secretion

B. Decrease inappropriate glucagon secretion

C. Slow gastric emptying

D. Increase urinary glucose excretion

8. A 110-kg patient with type 2 diabetes mellitus is taking insulin glargine 82 units at bedtime and scheduled doses of 12 units of insulin apart three times a day before each meal plus additional correction doses of insulin aspart for hyperglycemia. The patient's BGs have consistently been in the 70-90 mg/dL (3.9-5.0 mmol/L) range in the morning before breakfast, pre-evening meal glucose is 100-130 mg/dL (5.6-7.2 mmol/L), and bedtime blood glucose (BG) readings between 200 and 250 mg/dL (11.1 and 13.9 mmol/L). The patient's A1C is currently 7.6% (0.076; 60 mmol/mol) with a goal less than 7% (0.07; 53 mmol/mol). The *next best* step would be to:

A. Give 6 units of insulin lispro at bedtime.

B. Increase the dose of insulin lispro before the evening meal.

C. Change the timing of the insulin glargine injection from bedtime to morning.

D. Increase the dose of insulin glargine by 10%. Continue to inject subcutaneously at bedtime.

9. An obese patient (weight = 104kg, BMI = 36.2 kg/m^2) with type 2 diabetes mellitus is taking 76 units of insulin degludec daily and insulin glulisine 18 units prior to each meal. Which of the following would be the most appropriate to determine a correction dose to treat hyperglycemia?

A. 1 extra unit of insulin glulisine will lower blood glucose by 6 mg/dL (0.3 mmol/L).

B. 1 extra unit of insulin glulisine will lower blood glucose by 14 mg/dL (0.8 mmol/L).

C. 1 extra unit of insulin glulisine will lower blood glucose by 25 mg/dL (1.4 mmol/L).

D. 1 extra unit of insulin glulisine will lower blood glucose by 60 mg/dL (3.3 mmol/L).

10. Which one of the following insulin products have a duration of action greater than 24 hours?

A. Insulin degludec (U-200)

B. Insulin glulisine (U-100)

C. Regular human insulin (U-500)

D. Neutralize protamine Hagedorn insulin (U-100)

11. A patient with type 2 diabetes has adopted several lifestyle changes. He has lost 15 lb (6.8 kg) in the past 3 months. All lab work, vital signs, and physical examination findings are normal except for mild nonproliferative retinopathy and chronic kidney disease (eGFR consistently between 35 and 50 mL/min/1.73 m^2 for the past year) with albuminuria. The patient's A1C today is 6.2% (0.062; 44 mmol/mol). The patient's current treatment

regimen includes metformin 500 mg BID with meals, lisinopril 40 mg daily, rosuvastatin 20 mg daily. Which of the following medication changes should be recommended today?

A. Start dapagliflozin

B. Discontinue metformin

C. Discontinue Lisinopril

D. Increase metformin dose

12. A patient is prescribed metformin 500 mg BID. She states she was diagnosed with gestational diabetes mellitus (GDM) but wants to avoid taking insulin. Which of the following is the most appropriate action to take at this time?

A. Switch metformin to the extended-release product because it is much better tolerated in pregnancy.

B. Call the prescriber to ask if metformin can switch to glyburide because it has more data in pregnancy.

C. Call the prescriber to switch metformin to human insulin because it is the only FDA-approved treatment option.

D. Make certain the patient is aware that metformin is not currently the drug of choice to treat gestational diabetes.

13. GM is a 59-year-old female here for evaluation of her diabetes. All labs are normal except that her A1C is currently 8.6% (0.086; 70 mmol/mol), vitals are normal, and weight is 196 lb (89 kg; BMI is 34 kg/m^2). Her goal A1C is less than 7.5% (0.075; 58 mmol/mol). She is currently taking metformin 1,000 mg twice daily and canagliflozin 300 mg daily. She has hypertension (current blood pressure is 134/78 mm Hg) and dyslipidemia (current LDL-C is 82 mg/dL [2.12 mmol/L]). She is engaged in regular physical activity most days and avoids simple carbohydrates. Which of the following treatment options would likely have the greatest therapeutic benefits for this patient?

A. Linagliptin 5 mg orally daily

B. Glimepiride 4 mg orally daily

C. Semaglutide 0.25 mg subcutaneously weekly for 4 weeks then 0.5 mg weekly

D. Levemir 20 units subcutaneously at bedtime and titrate dose to achieve fasting blood glucose less than 90 mg/dL (5.0 mmol/L)

14. A 60-year-old overweight patient presents for diabetes follow-up. He has had type 2 diabetes for 10 years and also has hypertension and newly diagnosed peripheral vascular disease. His A1C is currently 7.6% (0.076; 60 mmol/mol) with a goal less than 7% (0.07; 53 mmol/mol). His current medications include metformin 1,000 mg twice daily, lisinopril 20 mg once daily, and amlodipine 10 mg once daily. Which of the following treatment options would likely have the greatest therapeutic benefit for this patient?

A. Dulaglutide

B. Glyburide

C. Insulin glargine U-100

D. Sitagliptin

15. An 84-year-old female has a history of type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, heart failure (NYHA Class 2), and osteoarthritis in the hands, hips, and knees. She resides in an assisted-living facility because she requires assistance with meal preparation and is at high risk for falls. She has some age-related forgetfulness but does not have any significant cognitive impairments. She is currently taking metformin 500 mg twice daily, sitagliptin 50 mg daily, and insulin glargine 20 units daily. Her current A1C is 9.6% (0.096; 81 mmol/mol). Which of the following is the most appropriate goal A1C for this patient?

A. A1C less than 6.5% (0.065; 48 mmol/mol)

B. A1C less than 7% (0.07; 53 mmol/mol)

C. A1C less than 8% (0.08; 64 mmol/mol)

D. A1C less than 10% (0.10; 86 mmol/mol)

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Type 1 diabetes is caused by an autoimmune process that destroys the β-cells in the pancreas, resulting in an absolute insulin deficiency. C-peptide, created by the cleavage of proinsulin, is a marker of endogenous insulin production. Therefore, C-peptide serum concentrations are very low or zero in patients with type 1 diabetes. While type 1 diabetes can occur at any age, it most commonly develops in childhood, with the peak incidence occurring in the early adolescent years prior to puberty (10-14 years old). See "Clinical Presentation" section.

2. **B.** Patients with type 2 diabetes have excessive hepatic glucose production, which is driven by inappropriate glucagon release (Answer C) and diminished sensitivity to insulin in the liver. Patients with type 2 diabetes have declining β-cell mass over time and typically have less than 50% of normal β-cell mass at the time of diagnosis (Answer A). Diminished incretin normal release following meals (Answer D) is commonly seen in patients with type 2 diabetes. See "Etiology and Pathophysiology" section.

3. **B.** The diagnosis of diabetes mellitus is based on evidence of abnormal plasma glucose concentrations. A hemoglobin A1C greater than 6.5% (0.065; 48 mmol/mol) is considered diagnostic for diabetes mellitus and suggests the patient's plasma glucose has been, on average, greater than 135 mg/dL (7.5 mmol/L) over the preceding 3 months. A fasting glucose reading above 124 mg/dL (6.9 mmol/L), measured on two separate occasions, also indicates the patient has diabetes. An OGTT can be used to diagnose diabetes as well, but the reading at 2 hours must be greater than 200 mg/dL (11.1 mmol/L) to be diagnostic for diabetes. While a random plasma glucose reading following a meal greater than 140 mg/dL (7.8 mmol/L) is abnormal, it is not sufficiently elevated to be diagnostic of diabetes. A random glucose reading must exceed 200 mg/dL (11.1 mmol/L), and the patient must also exhibit classic symptoms of diabetes such as polyuria, polydipsia, or weight loss. See Table 94-4.

4. **B.** This patient is most likely to have type 2 diabetes. Although genetics also influence the development of type 1 diabetes, it is far less inheritable than type 2 diabetes. Given there are multiple family members diagnosed with diabetes, there appears to be a strong inherence pattern that is suggestive of type 2 diabetes, MODY, or LADA. Given that the patient's father was able to use oral anti-diabetes medications for several years to achieve good glycemic control, it indicates that he does not have type 1 DM or LADA. Likewise, given that his sister has been able to achieve good glycemic control with weight loss and regular physical activity without medications, it suggests insulin resistance is a major component of this inheritable cause of diabetes and, thus, it is unlikely to be type 1 DM or LADA. While MODY is a possible etiology of diabetes, the fact that his father was diagnosed at age 44 years old makes this a less likely cause. MODY is generally diagnosed in early adulthood and generally does not require insulin therapy. See "Etiology and Pathophysiology" section.

5. **D.** Based on the patient's daily insulin requirements (>300 units/day), switching to a concentrated insulin product can reduce the number of injections required each day and may lead to improved glycemic control. U-500 insulin, given in two or three divided daily doses, can be used in place of both basal and prandial insulins. If the patient is near the glycemic goal, the total daily dose of insulin is typically reduced by 5% to 10% and re-titrated to achieve good glycemic control. Using insulin lispro (Answer B) would be inappropriate because it is a rapid-acting insulin given to reduce the postprandial glucose surge that occurs after meals and would do little to address basal insulin needs. The dose of insulin glargine (Answer A) would be insufficient to control this patient's blood glucose (in the absence of a prandial insulin), and, as monotherapy, it would not cover prandial insulin needs. The dose of insulin degludec (Answer C) is likely excessive, and, as monotherapy, it would not cover prandial insulin needs.

6. **A.** While some medication classes are associated with the development of heart failure (eg, thiazolidinediones, dipeptidyl peptidase-4 inhibitors), the SGLT-2 inhibitors appear to protect patients against the development of heart failure. Modest weight loss is a common and expected effect of the SGLT-2 inhibitors. Although uncommon, dizziness or lightheadedness can occur if a patient develops orthostatic hypotension due to vascular volume loss. Genitourinary tract infections, including urinary tract infections and candidiasis, were reported in 3% to 5% of patients who used an SGLT-2 inhibitor in clinical trials.

7. **D.** The GLP-1 receptor agonists mimic the action of endogenous GLP-1. They stimulate insulin secretion from pancreatic β-cells in a glucose-

dependent manner. In addition, during hyperglycemia, GLP-1 RAs reduce inappropriately elevated levels of glucagon, which results in decreased hepatic glucose output. These agents also have a direct effect on the stomach through the autonomic nervous system to slow gastric emptying, thereby reducing meal-related glucose excursions. Additionally, agents that penetrate the blood-brain barrier increase satiety via the central nervous system. These actions result in a reduction in both glucose and weight. GLP-1 RAs also potentially preserve pancreatic β-cell function and protect against cytokine-induced apoptosis. They do not act on the kidney. The SGLT-2 inhibitors increase urinary glucose excretion.

8. **B.** Given that the patient's blood glucose is elevated at bedtime but is within acceptable ranges in the morning and prior to dinner meal, the best strategy is to increase the prandial insulin dose prior to the evening meal. While administering a dose of rapid-acting insulin at bedtime would "correct" the elevated glucose readings, it does not prevent hyperglycemia, and it may lead to nocturnal hypoglycemia, overcorrecting the elevated blood glucose while the patient is sleeping. Changing the insulin glargine dose from bedtime to morning is unlikely to have the desired effect as the effects of insulin glargine typically last 20 to 24 hours and largely impact fasting glucose readings. Increasing the dose of insulin glargine would potentially result in nocturnal hypoglycemia as the patient's pre-breakfast fasting glucose readings are already within the goal range.

9. **B.** The patient is currently taking 130 units of insulin per day. The total daily dose of insulin is determined by adding all insulin doses administered. In this case, the patient is taking 76 units of insulin degludec plus 18 units of insulin glulisine prior to each meal or 54 units, for a total of 130 units. To estimate the correction or sensitivity factor, many practitioners use the rule of 1,800 when rapid-acting insulin is used for correction doses. To calculate the sensitivity factor, 1,800 is divided by the total daily dose of insulin (130 units). 1,800/130 = 13.8 or, rounding up, 14. Thus, 1 unit of insulin is anticipated to lower the blood glucose by approximately 14 mg/dL (0.8 mmol/L).

10. **A.** The duration of effect for insulin degludec is consistently greater than 24 hours. Insulin glulisine is a rapid-acting insulin with a typical duration of effect of around 5 to 6 hours. Regular U-500 human insulin has a duration of effect similar to NPH insulin—approximately 12 to 14 hours. See Table 94-7.

11. **A.** Dapagliflozin and other SGLT-2 inhibitors are effective at slowing the progression of CKD in patients with eGFR levels less than 60 mL/min/1.73 m^2 and/or albuminuria. The ADA guidelines recommend initiating an SGLT-2 inhibitor in this patient population independent of A1C, target A1C, or metformin use. Metformin can be used in patients with an eGFR less than 45 mL/min/1.73 m^2 with close monitoring of kidney function but should be discontinued if the eGFR drops below 30 mL/min/1.73 m^2. Some expert recommendations suggest using a lower dose (eg, 500 mg twice daily) in this setting. Based on the current A1C and kidney function, an increased dose is not warranted. Lisinopril is commonly used in patients with kidney insufficiency, but kidney function must be monitored regularly to be certain the serum creatinine does not change significantly (>30% increase) after treatment initiation or dose change. In this case, there would be no reason to discontinue therapy. Rosuvastatin can be safely used in patients with kidney impairment.

12. **D.** Insulin therapy is the drug-of-choice to control blood glucose in women with gestational diabetes. There is limited but reasonably compelling data demonstrating that metformin is safe and effective to use in pregnant women. It is unknown if the potential for fetal harm is greater with metformin use when compared to insulin therapy. There is no compelling reason to switch metformin to glyburide, and the risk of maternal hypoglycemia would be greater with glyburide use. While some patients tolerate the extended-release formulation better than the immediate-release product, pregnant women do not appear to be any more or less likely to tolerate the immediate-release product when compared to other populations. While it is true insulin is the only FDA-approved treatment for gestation diabetes, this does not preclude the off-label use of metformin for this indication. However, the patient should be made aware that metformin is not the drug of choice during pregnancy, and the risk of fetal complication is not yet fully understood. See "Pregnant Women" in the "Special Populations" section.

13. **C.** While all of these options would improve this patient's glycemic control, semaglutide (and other GLP-1 receptor agonists) is more likely to promote weight loss. Basal insulin (insulin detemir) can be titrated to goal and thus would be the best option in a patient with very poor glycemic control (eg, A1C >10.0% [0.10; 86 mmol/mol]). Unfortunately, baseline insulin can promote weight gain and cause hypoglycemia. Linagliptin, while it is weight neutral, is less potent in terms of lower blood glucose and is unlikely to get this patient to goal. Glimepiride is associated with weight gain and hypoglycemia; thus, it is a less attractive option for this patient.

14. **A.** This patient has uncontrolled diabetes with an A1C of 7.9% (0.079; 63 mmol/mol), so additional glucose-lowering medication is warranted. He also has established ASCVD (peripheral vascular disease) and is overweight. A GLP-1 receptor agonist would be the most appropriate treatment option as it has good glucose-lowering efficacy, induced weight loss, and has evidence of reducing major adverse cardiovascular events in patients with established ASCVD. Insulin and sulfonylureas such as glyburide can cause weight gain. Sitagliptin, a DPP-4 inhibitor, is weight neutral. In

addition, none of those options have CV benefits.

15. **C.** In older adults with multiple comorbidities, relaxed glycemic goals are appropriate. Thus, an A1C goal of 8.0% (0.080; 64 mmol/mol) would be appropriate for this patient. If this patient had significant cognitive impairments or a life-limiting illness (eg, malignancy, NYHA Class 4 heart failure), reliance on an A1C is no longer recommended, and routine BG monitoring should be used instead with a goal of maintaining the BG between 100 and 180 mg/dL (5.6 and 10.0 mmol/L) throughout the day. An A1C goal greater than 9.0% (0.090; 75 mmol/mol) would likely cause the patient to have significant symptoms such as frequent urination as well as increase the risk of falls due to orthostatic hypotension and urinary tract infections due to glycosuria. A more aggressive A1C goal of less than 7% or 6.5% (0.070 or 0.065; 53 or 48 mmol/mol) is unlikely to provide long-term benefits to this patient and would increase her risk of hypoglycemia which is more difficult to detect in older adults and may accelerate cognitive decline. See Table 94-6 for Goals of Therapy.