Chapter 19: Diabetes Mellitus

INTRODUCTION

- *Diabetes mellitus* (DM) is a group of metabolic disorders characterized by chronically elevated blood glucose (BG) and abnormal carbohydrate, fat, and protein metabolism. Without effective treatment, DM can lead to acute complications such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS). Chronic hyperglycemia can cause microvascular, macrovascular, and neuropathic complications.

PATHOPHYSIOLOGY

- Type 1 DM (5%–10% of cases) usually results from autoimmune destruction of pancreatic β-cells, leading to absolute deficiency of insulin. It usually presents in children and adolescents but can occur at any age. The disorder is believed to be initiated by exposure to an unknown environmental trigger in a genetically susceptible individual. The autoimmune process is mediated by macrophages and T lymphocytes with autoantibodies to β-cell antigens (eg, islet cell antibody, insulin antibodies). Amylin (a hormone cosecreted from pancreatic β-cells with insulin) is also deficient in type 1 DM due to β-cell destruction. Amylin suppresses inappropriate glucagon secretion, slows gastric emptying, and causes central satiety.

  ✔ After the initial diagnosis, a period of transient remission called the “honeymoon” phase may occur, during which insulin doses can be reduced or withdrawn before continued β-cell destruction requires lifelong insulin replacement therapy.

- Type 2 DM (90%–95% of cases) is characterized by multiple defects:

  ✔ *Impaired insulin secretion*: β-cell mass and function are both reduced, and β-cell failure is progressive.

  ✔ *Reduced incretin effect*: Normally, the gut incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are released and stimulate insulin secretion in response to a meal. Patients with type 2 DM have a reduced incretin effect due to decreased concentrations of or resistance to the effects of incretin hormones.

  ✔ *Insulin resistance*: This is manifested by excessive hepatic glucose production, decreased skeletal muscle uptake of glucose, and increased lipolysis and free fatty acid production.

  ✔ *Excess glucagon secretion*: This occurs because type 2 DM patients fail to suppress glucagon in response to meals because of GLP-1 resistance/deficiency and insulin resistance/deficiency, which directly suppress glucagon.

  ✔ *Sodium-glucose cotransporter-2 (SGLT-2) upregulation in the kidney*: This increases reabsorption of glucose by proximal renal tubular cells, which further contributes to hyperglycemia.

- *Gestational diabetes* (GDM) is DM that occurs in women during pregnancy.

- Less common causes of DM (1%–2%) include maturity onset diabetes of the young (MODY), genetic syndromes (eg, Down syndrome), endocrine disorders (eg, acromegaly, Cushing syndrome), pancreatic exocrine dysfunction, infections, and medications (eg, glucocorticoids, thiazides, niacin, atypical antipsychotics).

- Microvascular complications include retinopathy, neuropathy, and nephropathy. Macrovascular complications include coronary heart disease (CHD), stroke, and peripheral vascular disease.

CLINICAL PRESENTATION

Type 1 Diabetes Mellitus

- Patients often have symptoms in the days or weeks preceding the diagnosis. The most common initial symptoms are polyuria, polydipsia, polyphagia, weight loss, fatigue, and lethargy.
- Individuals are often thin and are prone to develop DKA in the absence of an adequate insulin supply; many patients initially present with DKA. Symptom onset can be triggered by infection, trauma, or psychological stress.

Type 2 Diabetes Mellitus

- Most patients are asymptomatic or have only mild fatigue at the time of diagnosis. Many patients are incidentally found to have type 2 DM after routine laboratory testing (eg, plasma glucose or A1C) or development of complications (eg, myocardial infarction, stroke).
- Because mild hyperglycemia may exist for years prior to the diagnosis, microvascular and macrovascular complications are often present at the time of diagnosis.
- Most patients are overweight or obese with an elevated waist:hip ratio.

DIAGNOSIS

- Normal fasting (no caloric intake for at least 8 hours) plasma glucose (FPG) is 70–99 mg/dL (3.9–5.5 mmol/L). Impaired fasting glucose (IFG) is FPG 100–125 mg/dL (5.6–6.9 mmol/L).
- Normal glucose tolerance based on a 2-hour post-load plasma glucose using the equivalent of 75 g anhydrous glucose dissolved in water (oral glucose tolerance test or OGTT) is <140 mg/dL (7.8 mmol/L). Impaired glucose tolerance (IGT) is OGTT 140–199 mg/dL (7.8–11.0 mmol/L).
- Normal A1C is 4%–5.6% (39–46 mmol/mol Hb). Increased risk of DM (prediabetes) is A1C 5.7%–6.4% (39–46 mmol/mol Hb).
- Criteria for diagnosis of DM include any one of the following:

  1. A1C ≥6.5% (48 mmol/mol Hb)
  2. FPG ≥126 mg/dL (7.0 mmol/L)
  3. OGTT ≥200 mg/dL (11.1 mmol/L)
  4. Random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis

  In the absence of unequivocal hyperglycemia, a diagnosis using criteria 1 through 3 requires two abnormal test results from the same sample or in two separate test samples.

- *Prediabetes* is a condition of abnormal BG that is not sufficiently high to meet the thresholds that define DM but often progresses to the diagnosis.
- Screening for type 1 DM in asymptomatic children or adults is not recommended due to low disease prevalence and the acute onset of symptoms. Screening for type 2 DM is recommended for asymptomatic 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 developing type 2 DM. All adults, even those without risk factors, should be screened every 3 years starting at 45 years old. Children at risk for developing type 2 DM should undergo screening every 3 years starting at age 10 years. Pregnant women should undergo risk assessment for GDM at the first prenatal visit; those with multiple risk factors for type 2 DM should be tested as soon as feasible. All women (even if the initial test was negative) should undergo testing at 24–28 weeks' gestation.

TREATMENT

- Goals of Treatment: The primary goal is to prevent or delay progression of long-term microvascular and macrovascular complications. Additional goals are to alleviate symptoms of hyperglycemia, minimize hypoglycemia and other adverse effects, minimize treatment burden, and maintain

quality of life. General glycemic targets for most nonpregnant adults with DM are listed in **Table 19-1**.

TABLE 19-1

Glycemic Target Recommendations for Most Nonpregnant Adults with Diabetes

Parameter	American Diabetes Association (ADA)	American Association of Clinical Endocrinologists (AACE)
A1C	<7.0% (53 mmol/mol Hb)	≤6.5% (48 mmol/mol Hb)
Fasting plasma glucose (FPG)	80–130 mg/dL (4.4–7.2 mmol/L)	<110 mg/dL (6.1 mmol/L)
Postprandial glucose (PPG)	<180 mg/dL (10 mmol/L)	<140 mg/dL (7.8 mmol/L)

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

Initial Assessment

- During the initial visit, perform a full medical evaluation to confirm the diagnosis, classify the type of diabetes, identify complications or potential comorbid conditions, and review previous treatments and risk factors in established patients.
- Review past medical, family, and social history as well as medication use, adherence, tolerability, and use of diabetes technology.
- Screen for psychosocial conditions, self-management education needs, and hypoglycemia.
- Perform a thorough physical exam (including height, weight, BMI, blood pressure, thyroid palpation, and foot exam) and laboratory evaluation (including A1C, lipid profile, liver function tests, serum creatinine, and eGFR).
- Calculate a 10-year ASCVD risk score.

Nonpharmacologic Therapy

- Medical nutrition therapy (MNT) involves an individually tailored nutrition plan. Implement a healthy meal plan that is moderate in calories and carbohydrates and low in saturated fat with all of the essential vitamins and minerals. Target an initial weight loss goal of at least 5% in all type 2 DM patients who are overweight or obese through calorie restriction. For individuals with type 1 DM, focus on physiologically regulating insulin administration rather than the amount and type of carbohydrates ingested.
- Aerobic exercise can improve insulin sensitivity, modestly improve glycemic control, reduce cardiovascular (CV) risk, contribute to weight control, and improve well-being. Physical activity goals include at least 150 min/week of moderate (50%–70% maximal heart rate) intensity exercise spread over at least 3 days/week with no more than 2 days between activity. Resistance/strength training is recommended at least 2 times/week for patients without proliferative diabetic retinopathy.
- Offer access to diabetes self-management education and support (DSME/S) programs to all patients. Such programs target self-care behaviors of healthy eating, being active, monitoring glucose levels, taking medications, problem-solving, reducing risk of complications, and healthy coping. Patients must be involved in decision making and have strong knowledge of the disease and associated complications.

Pharmacologic Therapy

Insulin

- 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, need for injections, weight gain, and treatment burden.

- All commercial insulin preparations are produced using recombinant DNA technology. “Human” insulins (NPH, regular) are recombinant DNA–derived human insulin, whereas 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 (SC) for chronic diabetes management, except for inhaled human insulin, which is a dry powder of regular insulin that is inhaled and absorbed through pulmonary tissue.
- The most commonly used insulin concentration is 100 units/mL (U-100); more concentrated insulins (U-200, U-300, U-500) may be considered for patients requiring larger doses. U-500 regular insulin is reserved for patients with extreme insulin resistance and is usually given two or three times a day.
- The pharmacokinetics of insulin products is characterized by their onset, peak, and duration of action (**Table 19-2**).
- *Basal insulin* (or 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. Options include the following insulins:

  ✔ **NPH** is the least ideal product because it has a distinct peak and a duration of action much less than 24 hours and usually requires twice-daily dosing.

  ✔ **Detemir** also has a peak and often lasts <24 hours; it can be given once daily in some patients but should be dosed twice daily at low doses (<0.3 units/kg).

  ✔ **Glargine U-100** is considered to be peakless and can usually be given once daily.

  ✔ **Glargine U-300** and **degludec U-100 or U-200** are longer acting-agents that have no peak and are given once daily.

  All basal insulins can achieve similar A1C reductions if dosed and titrated properly, but the longer-acting products have a lower risk of hypoglycemia (particularly nocturnal hypoglycemia) and may result in less glucose variability. However, they are more expensive.

- *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 for patients with type 2 DM, whereas patients with type 1 DM require a combination of basal and bolus insulin to achieve adequate glycemic control. Bolus insulin options include:

  ✔ **Aspart**, **lispro**, and **glulisine**, the rapid-onset, short-duration insulins

  ✔ **Inhaled human insulin** and **fast-acting insulin aspart (Fiasp)**, the ultra-rapid onset insulins

  Rapid-acting insulins offer a faster onset and shorter duration of action than **regular insulin**, and ultra-rapid acting insulins offer an even faster onset; this may more closely mimic prandial endogenous insulin release. Rapid-acting insulins have a modestly lower risk of hypoglycemia than regular insulin. All prandial insulins can be used effectively, but cost differences can be substantial.

- Various premixed insulin products containing both a basal and a prandial component are also available for patients who require fewer injections or a simpler regimen (**Table 19-2**). However, these products are limited by fixed mixed formulations, which can make it challenging to tailor the dosing regimen.
- The insulin dose must be individualized. In type 1 DM, the average daily requirement is 0.5–0.6 units/kg, with approximately 50% given as basal insulin and the remaining 50% dedicated to meal coverage. During the honeymoon phase, requirements may fall to 0.1–0.4 units/kg. Higher doses are often needed during acute illness or with ketosis.
- Hypoglycemia is the most common adverse effects of insulin therapy. Insulin also causes dose-dependent weight gain, which occurs predominantly in truncal fat. Injection site reactions may include redness, pain, itching, urticaria, edema, and inflammation. SC administration can result in lipoatrophy or lipohypertrophy, which can be prevented by routinely rotating injection sites. Inhaled human insulin can cause cough and upper respiratory infections, and it is contraindicated in chronic obstructive pulmonary disease and asthma due to bronchospasm risk. Because inhaled insulin has been associated with a small decline in pulmonary function, patients should have spirometry tests performed at

baseline, 6 months, and annually thereafter.

TABLE 19-2

Pharmacokinetics of Select Insulins Administered Subcutaneously

Type of Insulin[a] by Generic (Brand) Name	Onset	Peak[b]	Duration[b]
Ultra-rapid acting			
Insulin aspart (Fiasp)	15–20 min[c]	90–120 min	5–7 hours
Insulin human—inhaled (Afrezza)	12 min	35–55 min	1.5–4.5 hours
Rapid-acting			
Insulin aspart (NovoLog)	10–20 min	30–90 min	3–5 hours
Insulin lispro U-100, U-200 (Humalog)			
Insulin glulisine (Apidra)			
Short-acting			
Regular (Humulin R, Novolin R)	30–60 min	2–4 hours	5–8 hours
Intermediate-acting			
NPH (Humulin N, Novolin N)	2–4 hours	4–10 hours	10–24 hours
Regular U-500 (Humulin R 500)	15 min	4–8 hours	13–24 hours
Long-acting			
Insulin detemir (Levemir)	1.5–4 hours	6–14 hours[d]	16–20 hours
Insulin glargine (Lantus, Basaglar)	2–4 hours	No peak	20–24 hours
Insulin glargine U-300 (Toujeo)	6 hours	No peak	36 hours
Insulin degludec U-100, U-200 (Tresiba)	1 hour	No peak	42 hours
Combination Products			
70% NPH/30% Regular (Humulin 70/30, Novolin 70/30)	30–60 min	Dual	10–16 hours
75% NPL, 25% lispro (Humalog 75/25)	5–15 min		10–16 hours
50% NPL, 50% lispro (Humalog 50/50)	5–15 min		10–16 hours
70% insulin aspart protamine, 30% insulin aspart (NovoLog 70/30)	5–15 min		15–18 hours

[a]U-100 unless otherwise noted.

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

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

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

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

Biguanides

- **Metformin** decreases hepatic glucose production and enhances insulin sensitivity in peripheral (muscle) tissues, allowing for increased glucose uptake into muscle cells.
- Metformin is recommended as first-line pharmacotherapy in patients with type 2 DM (unless a contraindication or intolerability exists) 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. It reduces A1C levels by 1.5%–2% (16–22 mmol/mol Hb) and FPG levels by 60–80 mg/dL (3.3–4.4 mmol/L) in drug-naïve patients with initial A1C values of approximately 9% (75 mmol/mol Hb). It does not cause weight gain and may lead to a modest (2–3 kg) weight loss. It has a low risk of hypoglycemia because it does not directly increase pancreatic insulin secretion. Metformin decreases plasma triglycerides and low-density lipoprotein cholesterol (LDL-C) by approximately 8%–15% and modestly increases high-density lipoprotein cholesterol (HDL-C) by 2%.
- Metformin frequently causes GI side effects (diarrhea, abdominal discomfort, stomach upset); these effects are usually dose-dependent, transient, mild, and can be minimized with slow dose titration and taking metformin with or immediately after meals. When initiating therapy, use a low dose (typically 500 mg) given with the largest meal. Then increase the dose in 500-mg increments over several weeks. Extended-release metformin may lessen some of the GI side effects, but a comparison of immediate-release vs extended-release metformin found no significant differences in rates of GI adverse effects.
- Metformin may cause a metallic taste and may lower vitamin B_{12} concentrations; B_{12} levels or methylmalonic acid should be measured annually or if a deficiency is suspected, with vitamin B_{12} supplementation given if indicated.
- Lactic acidosis occurs rarely, usually in the setting of severe illness or acute kidney injury. The risk may increase in moderate-to-severe renal insufficiency or tissue hypoperfusion states such as acute heart failure (HF), excessive alcohol intake, and hepatic impairment. Because symptoms are often nonspecific, the diagnosis must be confirmed by laboratory measurement of high lactic acid levels and acidosis.
- Metformin is renally excreted and accumulates in renal insufficiency; it is contraindicated in patients with eGFR <30 mL/min/1.73 m^2 and should be used with caution in patients with milder renal insufficiency. Metformin initiation is not recommended in patients with eGFR 30–45 mL/min/1.73 m^2 but can be continued with increased renal function monitoring; a reduction of 50% of maximal dose may be warranted. Due to the risk of acute renal failure with use of IV contrast dye, withhold metformin therapy starting the day of the procedure and resume it 2–3 days later if normal renal function has been documented.
- Metformin can be used in combination with any other antihyperglycemic therapy and is often continued when insulin therapy is initiated. The target metformin dose is 1000 mg twice daily or 2000 mg daily if the extended-release product is used. The minimal effective dose is 1000 mg/day. See **Table 19-3** for metformin dosing recommendations.
- Numerous combination products containing metformin as well as combinations of other drug classes are available (**Table 19-4**).

TABLE 19-3

Dosing Recommendations for Oral Medications Used to Treat Type 2 Diabetes

Generic (Brand) Name	Starting Dose	Usual Recommended Dose	Maximal dose (mg/day)	Dosing/Use in Renal Insufficiency[a]
Biguanides				
Metformin (Glucophage)	500 mg once or twice daily or 850 mg once daily, titrate to target dose as tolerated	1000 mg twice daily	2550	Do not initiate if eGFR 30–45; Do not use if eGFR <30
Metformin XR	500–1000 mg once daily, titrate to target dose as tolerated	2000 mg once daily	2500	Do not initiate if eGFR 30–45; Do not use if eGFR <30
Sulfonylureas (first generation)				
Chlorpropamide	250 mg once daily (100 mg once daily in older adults)	100–500 mg once daily	750	Consider alternative agent or initiate conservatively at 100 mg in renal 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	1000	Consider alternative agent or initiate conservatively at 100 mg in renal insufficiency to avoid hypoglycemia
Tolbutamide	1000–2000 mg once daily (250–500 mg once daily in older adults)	1000–2000 mg once daily	3000	Consider alternative agent or initiate conservatively in renal insufficiency to avoid hypoglycemia
Sulfonylureas (second generation)				
Glimepiride (Amaryl)	1–2 mg once daily (1 mg once daily in older adults)	4 mg once daily	8	Initiate conservatively at 1 mg in renal insufficiency to avoid hypoglycemia
Glipizide (Glucotrol)	5 mg once daily (2.5 mg daily in older adults)	5–10 mg once daily	40	Initiate conservatively at 2.5 mg in renal insufficiency to avoid hypoglycemia
Glipizide XL (Glucotrol XL)	5 mg once daily (2.5 mg once daily in older adults)	5–10 mg once daily	20	Initiate conservatively at 2.5 mg in renal insufficiency to avoid hypoglycemia
Glyburide (Diabeta)	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 renal insufficiency to avoid hypoglycemia
Glyburide micronized (Glynase)	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 renal insufficiency to avoid hypoglycemia
Meglitinides				
Nateglinide (Starlix)	120 mg three times daily before meals	120 mg three times daily before meals	360	No adjustment required

Repaglinide (Prandin)	1–2 mg three times daily before meals (0.5 mg before meals if A1C <8% [64 mmol/mol Hb])	2–4 mg three times daily before meals	16	Initiate conservatively at 0.5 mg before meals if CrCl 20–40 mL/min (0.33–0.67 mL/sec)
Thiazolidinediones				
Pioglitazone (Actos)	15 mg once daily	30 mg once daily	45	No dose adjustment required
Rosiglitazone (Avandia)	4 mg once daily or in two divided doses	4 mg once daily or in two divided doses	8	No dose adjustment required
α-Glucosidase inhibitors				
Acarbose (Precose)	25 mg once to three times daily with the first bite of a meal	50 mg once to three times daily with meals	300	Avoid if CrCl <25 mL/min (0.42 mL/sec)
Miglitol (Glyset)	25 mg once to three times daily with the first bite of a meal	50 mg once to three times daily with meals	300	Avoid if CrCl <25 mL/min (0.42 mL/sec)
Sodium-glucose transporter (SGLT)-2 inhibitors				
Canagliflozin (Invokana)	100 mg once daily, taken before the first meal of the day	100–300 mg once daily	300	100 mg once daily if eGFR 45–60; Avoid if eGFR <45
Dapagliflozin (Farxiga)	5 mg once daily in the morning with or without food	5–10 mg once daily	10	Avoid if eGFR <60
Empagliflozin (Jardiance)	10 mg once daily in the morning with or without food	10–25 mg once daily	25	Avoid if eGFR <30
Ertugliflozin (Steglatro)	5 mg once daily in the morning with or without food	5–15 mg once daily	15	Avoid if eGFR<60
Dipeptidyl peptidase (DPP)-4 inhibitors				
Alogliptin (Nesina)	25 mg once daily with or without food	25 mg once daily	25	12.5 mg once daily if CrCl 30–60 mL/min (0.5–1.0 mL/sec); 6.25 mg once daily if CrCl <30 mL/min (0.5 mL/sec)
Linagliptin (Tradjenta)	5 mg once daily with or without food	5 mg once daily	5	No dose adjustment needed
Saxagliptin (Onglyza)	2.5–5 mg once daily with or without food	5 mg once daily	5	2.5 mg once daily if eGFR ≤50
Sitagliptin (Januvia)	100 mg once daily with or without food	100 mg once daily	100	50 mg once daily if eGFR 30–50; 25 mg once daily if eGFR <30

Bile acid sequestrants				
Colesevelam (Welchol)	1.875 g twice daily or 3.75 g once daily with meals	1.875 g twice daily or 3.75 g once daily with meals	3.75 g/day	No dose adjustment needed
Dopamine agonists				
Bromocriptine (Cycloset)	0.8 mg once daily, taken within 2 hours after waking in the morning with food	1.6–4.8 mg once daily	4.8	No dose adjustment needed

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

TABLE 19-4

Combination Drug Products for Type 2 Diabetes

Drug Classes	Drug Combination		Brand Name
Biguanide and sulfonylurea	Metformin	Glipizide	Metaglip[a]
	Metformin	Glyburide	Glucovance[a]
Biguanide and meglitinide	Metformin	Repaglinide	Prandimet[a]
Biguanide and thiazolidinedione	Metformin	Pioglitazone	Actoplus Met[a], Actoplus Met XR
	Metformin	Rosiglitazone	Avandamet[a]
Biguanide and DPP-4 inhibitor	Metformin	Alogliptin	Kazano
	Metformin	Linagliptin	Jentadueto, Jentadueto XR
	Metformin	Saxagliptin	Kombiglyze XR
	Metformin	Sitagliptin	Janumet, Janumet XR
Biguanide and SGLT-2 inhibitor	Metformin	Canagliflozin	Invokamet, Invokamet XR
	Metformin	Dapagliflozin	Xigduo XR
	Metformin	Empagliflozin	Synjardy, Synjardy XR
	Metformin	Ertugliflozin	Segluromet
Thiazolidinedione and sulfonylurea	Pioglitazone	Glimepiride	Duetact[a]
	Rosiglitazone	Glimepiride	Avandaryl
Thiazolidinedione and DPP-4 inhibitor	Pioglitazone	Alogliptin	Oseni
SGLT-2 inhibitor and DPP-4 inhibitor	Dapagliflozin	Saxagliptin	Qtern
	Empagliflozin	Linagliptin	Glyxambi
	Ertugliflozin	Sitagliptin	Steglujan
Basal insulin and GLP-1 receptor agonist	Insulin glargine U-100	Lixisenatide	Soliqua
	Insulin degludec U-100	Liraglutide	Xultophy

[a]Available as generic product.

XR, extended release.

Sulfonylureas

- Sulfonylureas enhance insulin secretion by binding to the sulfonylurea receptor SUR1 on pancreatic β-cells. First-generation agents (**chlorpropamide**, **tolazamide**, and **tolbutamide**) are lower in potency than second-generation drugs (**glyburide**, **glipizide**, and **glimepiride**), and are rarely used due to a higher risk of adverse effects.
- All sulfonylureas are equally effective in lowering BG when given in equipotent doses. On average, the A1C falls by 1.5%–2% (16–22 mmol/mol Hb) with FPG reductions of 60–70 mg/dL (3.3–3.9 mmol/L) in drug-naïve patients.
- Sulfonylureas are widely used because they have an extensive record of safety and effectiveness, are given orally, and are inexpensive. However, current treatment guidelines either discourage their use or suggest caution due to the risk of hypoglycemia and weight gain. In addition, tachyphylaxis to the insulin secretion effect occurs, leading to poor long-term durability of response in most patients.
- The most common side effect is hypoglycemia. Patients who skip meals, exercise vigorously, or lose a substantial amount of weight are more prone to hypoglycemia. Sulfonylureas with long durations of action and those with active metabolites should be used with extreme caution in older patients and those with renal insufficiency due to the high risk of hypoglycemia. Weight gain is common (typically 1–2 kg). Patients with sulfa allergy rarely experience crossreactivity with sulfonylureas.
- See **Table 19-3** for sulfonylurea dosing information.

Thiazolidinediones (TZDs)

- TZDs bind to the peroxisome proliferator activator receptor-γ (PPAR-γ) located primarily on fat and vascular cells, enhancing insulin sensitivity in muscle, liver, and fat tissues.
- At maximal doses, **pioglitazone** and **rosiglitazone** reduce A1C by 1%–1.5% (11–22 mmol/mol Hb) and FPG by 60–70 mg/dL (3.3–3.9 mmol/L), and they have high durability over time. Maximum effects may not be seen until 3–4 months of therapy.
- 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.
- Pioglitazone decreases plasma triglycerides by 10%–20%, whereas rosiglitazone tends to have no effect. Pioglitazone does not significantly increase LDL-C, whereas rosiglitazone may increase LDL-C by 5%–15%. Both drugs increase HDL-C, but the magnitude may be greater with pioglitazone.
- Fluid retention may occur due to peripheral vasodilation and improved insulin sensitization in the kidney with increased sodium and water retention. This may result in peripheral edema (4%–5% of patients with monotherapy; 15% or more when combined with insulin), HF, hemodilution of hemoglobin and hematocrit, and weight gain. Edema is dose related and if not severe may be managed by dose reduction in most patients. TZDs are contraindicated in patients with New York Heart Association Class III or IV HF and should be used with caution in patients with Class I or II HF.
- Weight gain is dose related and results from both fluid retention and fat accumulation; a gain of 4 kg is not uncommon, and higher gains may require drug discontinuation. TZDs have also been associated with an increased fracture rate in the upper and lower limbs of postmenopausal women. An increased risk of bladder cancer is controversial.
- See **Table 19-3** for TZD dosing information.

Glucagon-like Peptide 1 Receptor Agonists (GLP1-RAs)

- **Dulaglutide**, **exenatide**, **exenatide XR**, **lixisenatide**, **liraglutide**, and **semaglutide** stimulate insulin secretion and suppress inappropriately high postprandial glucagon secretion, decreasing hepatic glucose output. They also slow gastric emptying, increase satiety, and cause weight loss (average 1–3 kg).
- Short-acting agents (exenatide, lixisenatide) predominantly lower postprandial glucose (PPG) levels, whereas long-acting agents (dulaglutide, liraglutide, exenatide XR, semaglutide) lower both FPG and PPG, but with larger effects on FPG. Evidence suggests that liraglutide and semaglutide

have the highest A1C and weight-lowering efficacy while exenatide and lixisenatide have the lowest.

- Liraglutide and semaglutide have demonstrated CV benefits in clinical trials. Liraglutide is FDA approved to reduce the risk of major adverse CV events in adults with type 2 DM and established atherosclerotic cardiovascular disease (ASCVD).
- GLP1-RAs are not currently recommended as first-line agents but can be used as monotherapy in patients who cannot tolerate or take first-line therapy. They are recommended second-line agents for patients with established ASCVD or chronic kidney disease (CKD) and those with a compelling need to avoid hypoglycemia or to avoid weight gain or induce weight loss. They can be used in combination with metformin, TZDs, sulfonylureas, SGLT-2 inhibitors, and basal insulin. They should not be used in combination with DPP-4 inhibitors due to similar mechanisms of action.
- The GLP1-RAs are administered SC and have important differences in efficacy, adverse effect rates, and dosing schedules (**Table 19-5**).
- The most common adverse effects of GLP1-RAs are nausea, vomiting, and diarrhea. These effects are dose related, so dose titration is recommended. They usually occur early in the treatment course and are mild and transient but may require drug discontinuation in some patients. Instruct patients to eat slowly and stop eating when satiated or nausea may worsen and cause vomiting. Injection site reactions and hypersensitivity reactions (including anaphylaxis and angioedema) have been reported.
- Because GLP1-RAs enhance insulin secretion in response to food intake, the risk of hypoglycemia is low when combined with metformin, SGLT-2 inhibitors, or a TZD. However, hypoglycemia may occur when combined with a sulfonylurea or insulin.

TABLE 19-5

Dosing Recommendations for Subcutaneous GLP-1 Receptor Agonists

Generic (Brand) Name	Dose[a]	Interval	Renal Dose/Use[b]
Exenatide (Byetta)	5–10 mcg	Twice daily (30–60 min before breakfast and dinner)	Avoid if eGFR <30
Lixisenatide (Adlyxin)	10–20 mcg	Once daily (1 hour before breakfast)	Limited experience in severe renal impairment; avoid if eGFR <15
Dulaglutide (Trulicity)	0.75–1.5 mg	Once weekly (at any time of day, with or without food)	Limited experience in severe renal impairment
Exenatide XR (Bydureon)	2 mg	Once weekly (at any time of day, with or without meals)	Avoid if eGFR <30
Liraglutide (Victoza)	0.6–1.8 mg	Once daily (with or without meals)	Limited experience in severe renal impairment
Semaglutide (Ozempic)	0.25–1 mg	Once weekly	No dose adjustment recommended

[a]All products require subcutaneous administration into the abdomen, thigh, or upper arm.

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

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

- **Alogliptin, linagliptin, saxagliptin,** and **sitagliptin** prolong the half-life of endogenously produced GLP-1 and GIP, thereby increasing

glucose-dependent insulin secretion from the pancreas and reducing inappropriate postprandial glucagon secretion, resulting in lower glucose levels without an increase in hypoglycemia when used as monotherapy. They do not alter gastric emptying, cause nausea, have significant effects on satiety, or cause weight gain/loss.

- DPP-4 inhibitors produce average A1C reductions of 0.5%–0.9% (6–10 mmol/mol Hb) when used at maximum doses. There are no clear differences in efficacy among agents in the class.
- DPP-4 inhibitors are considered second- or third-line therapy. Advantages include once-daily dosing, oral administration, weight neutrality, low risk of hypoglycemia, and good tolerability. However, they have less A1C lowering efficacy than other second-line medication classes and are expensive.
- Adverse effects are uncommon and include stuffy, runny nose; headache; and upper respiratory tract infections. The labeling of saxagliptin and alogliptin includes information about increased risk of hospitalizations for HF. The FDA has also issued a warning on the risk of severe joint pain with DPP-4 inhibitors. Pancreatitis appears to be an established but rare safety concern.
- There is no need to titrate the dose of DPP-4 inhibitors; however, renal dose adjustments are required for alogliptin, saxagliptin, and sitagliptin (**Table 19-3**).

Sodium-Glucose Cotransporter-2 Inhibitors

- **Canagliflozin**, **dapagliflozin**, **empagliflozin**, and **ertugliflozin** reduce plasma glucose by preventing the kidneys from reabsorbing glucose back into the bloodstream, leading to increased glucose excretion in the urine. SGLT-2 inhibitors lower both FPG and PPG and are effective even in the absolute absence of insulin.
- SGLT-2 inhibitors reduce A1C by 0.5%–1% (6–11 mmol/mol Hb) and appear to be more effective in patients with higher baseline A1C levels. Renal impairment decreases the efficacy of SGLT-2 inhibitors.
- SGLT-2 inhibitors are second-line agents that can be added to metformin or other second-line agents. They are not recommended as first-line agents but can be used as monotherapy in patients who cannot tolerate or take first-line therapy. They are recommended for patients with established ASCVD or CKD and those with a need to avoid hypoglycemia or weight gain or loss. They are unlikely to cause hypoglycemia unless combined with medications such as sulfonylureas, meglitinides, or insulin.
- Both empagliflozin and canagliflozin reduced major adverse CV events in large clinical trials, and empagliflozin is FDA approved to reduce the risk of CV death in adults with type 2 DM and established ASCVD.
- The most common adverse effect is genital mycotic infections, which are more common in women and uncircumcised men. There is also a slightly increased risk of urinary tract infections. Polyuria, dehydration, dizziness, or hypotension may occur because of the osmotic diuresis effects. Concomitant diuretic use may increase the risk of orthostatic hypotension and electrolyte abnormalities. Older adults and patients with stage 4 or 5 CKD are not optimal treatment candidates. Other potential safety concerns include ketoacidosis, amputations, fractures, and Fournier gangrene.
- The SGLT-2 inhibitors should be started at a low dose with assessment of volume status, adverse effects, and renal function. The dose may be titrated in patients who are tolerating the drug well and require additional glucose control (**Table 19-3**).

α-Glucosidase Inhibitors

- **Acarbose** and **miglitol** delay the breakdown of sucrose and complex carbohydrates in the small intestine, prolonging carbohydrate absorption. The net effect is reduction in PPG (40–50 mg/dL; 2.2–2.8 mmol/L) with relatively unchanged FBG. A1C lowering is modest, with average A1C reductions of 0.3%–1%.
- Good candidates for these drugs are patients who are near target A1C levels with near-normal FPG but high PPG levels.
- The most common side effects are flatulence, abdominal pain, and diarrhea, which can be reduced by slow dosage titration (**Table 19-3**).

Meglitinides

- **Nateglinide** and **repaglinide** stimulate insulin secretion from pancreatic β-cells by binding to a site adjacent to the sulfonylurea receptor. They are similar to sulfonylureas except that they have a faster onset and shorter duration of action. As monotherapy, they reduce PPG excursions and reduce A1C by 0.8%–1% (9–11 mmol/mol Hb).
- Similar to sulfonylureas, the main side effects are hypoglycemia and weight gain.
- Their role in therapy is unclear due to lack of clinical evidence. They are not included in the American Diabetes Association (ADA) treatment algorithm. They may be used in patients with renal insufficiency and may be a good option for patients with erratic meal schedules. However, multiple daily dosing may decrease adherence.
- Meglitinides should be taken by mouth with each meal, initiated at a low dose, and titrated over time until glycemic control is achieved (**Table 19-3**).

Bile Acid Sequestrants

- **Colesevelam** binds bile acid in the intestinal lumen, decreasing the bile acid pool for reabsorption. Its mechanism in lowering plasma glucose levels is unknown, and its role in therapy is unclear.
- A1C lowering efficacy is modest. It reduces LDL-C in patients with type 2 DM by 12%–16% but has not been proven to reduce CV morbidity or mortality. Colesevelam is weight neutral and has a low risk of hypoglycemia. 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.
- The most common side effects are constipation and dyspepsia; colesevelam should be taken with a large amount of water. Colesevelam has multiple absorption-related drug–drug interactions. See **Table 19-3** for dosing information.

Dopamine Agonists

- **Bromocriptine mesylate** is FDA approved for treatment of type 2 DM. The mechanisms by which it improves glycemic control are unknown but may involve improved hepatic insulin sensitivity and decreased hepatic glucose output.
- The A1C lowering efficacy is modest, and its role in the treatment of type 2 DM is unclear.
- Common side effects include nausea, vomiting, constipation, fatigue, headache, dizziness, and asthenia. Somnolence and orthostatic hypotension may also occur.

Amylin Analogs

- **Pramlintide** (Symlin) is a synthetic amylin analog that reduces glucagon secretion, slows gastric emptying, and increases satiety. It was the first noninsulin agent approved for patients with type 1 DM.
- Pramlintide lowers both PPG levels and A1C. The average A1C reduction is about 0.6% (7 mmol/mol Hb) in patients with type 2 DM and 0.4%–0.5% (5–6 mmol/mol Hb) in type 1 DM.
- It is used primarily in type 1 DM as adjunctive therapy for patients who are not achieving PPG goals despite maximizing mealtime insulin doses. It can also decrease weight and may allow for lower mealtime insulin doses.
- The most common adverse effects are nausea, vomiting, and anorexia. It does not cause hypoglycemia when used alone, but hypoglycemia can occur when used with insulin. To minimize the risk of severe hypoglycemia, empirically reduce the mealtime insulin dose by 30%–50% when pramlintide is initiated.
- In type 2 DM, the starting dose is 60 mcg SC prior to meals, titrated to the maximally recommended 120-mcg SC dose as tolerated and warranted based on PPG levels. In type 1 DM, dosing starts at 15 mcg SC prior to meals and can be titrated up in 15-mcg increments to a maximum of 60 mcg

SC prior to each meal, if tolerated.

Treatment of Hyperglycemia in Type 2 Diabetes

- Upon diagnosis, assess the patient's current lifestyle, existing comorbidities, A1C, age, weight, presence or absence of symptoms, motivation, cultural preferences, health literacy level, and cost limitations. Set a patient-specific A1C target and discuss it with the patient.
- Implement comprehensive lifestyle modifications with MNT, physical activity, weight loss if obese, smoking cessation, and psychologic support upon diagnosis and reinforce them at every visit. All patients should be offered access to ongoing DSME/S programs.
- Initiate metformin as first-line therapy in patients without contraindications or tolerability issues. Start with a low dose and titrate to the maximum effective dose over time to improve tolerability.
- If the initial A1C is close to goal (eg, ≤7.5% [58 mmol/mol Hb]) consider initial treatment with lifestyle modifications alone if the patient is motivated.
- Consider starting two medications (metformin plus a second agent) if the initial A1C is >1.5% (16 mmol/mol Hb) higher than the target A1C.
- Consider early introduction of basal insulin in patients with very high A1C levels (>10% [86 mmol/mol Hb]), symptoms of hyperglycemia, or evidence of catabolism (eg, weight loss).
- See patients at least every 3 months if they are not meeting their goals and at least every 6 months if they are meeting goals. At those times, check an A1C level, assess medication adherence, and reinforce lifestyle recommendations. Add additional therapy if glucose targets have not been met.
- For patients maximized on metformin therapy but with A1C levels above the target, add a second-line antihyperglycemic agent. The ADA Standards of Care identify six drug classes to consider: (1) DPP-4 inhibitors, (2) GLP1-RAs, (3) SGLT-2 inhibitors, (4) sulfonylureas, (5) TZDs, and (6) basal insulin. Patient-specific factors to consider in medication selection include the individualized A1C target and presence of comorbidities (eg, ASCVD, HF, CKD, obesity). Drug-specific factors to consider include glucose-lowering efficacy, impact on comorbidities, effect on weight and hypoglycemia risk, side-effect profile, ease of use, and cost. Recommendations based on patient-specific comorbidities and other factors include:

  ✔ Established ASCVD or CKD: SGLT-2 inhibitor (eg, empagliflozin) or GLP1-RA (eg, liraglutide) with proven CV benefit.

  ✔ Established ASCVD and HF: SGLT-2 inhibitor with proven benefit in reducing HF progression. Avoid TZDs in patients with HF.

  ✔ CKD (with or without ASCVD): SGLT-2 inhibitor with proven benefit in reducing CKD progression.

  ✔ Need to minimize weight gain or promote weight loss in patients without ASCVD or CKD: GLP1-RA or SGLT-2 inhibitor. If these agents cannot be used, use a weight-neutral medication such as a DPP-4 inhibitor. Avoid sulfonylureas, insulin, and TZDs due to weight gain.

  ✔ Compelling need to minimize hypoglycemia: DPP-4 inhibitor, GLP1-RA, SGLT-2 inhibitor, or TZD could be added to metformin.
- If the A1C target is not achieved after 3 months of dual therapy or if the patient did not tolerate the selected drug(s), then triple therapy is warranted, adding a drug from another class.
- People with type 2 DM can often be managed with oral medications for years before injectable medications are needed. Insulin is recommended for extreme (A1C >10% [86 mmol/mol Hb]) or symptomatic hyperglycemia. Otherwise, GLP-1 RAs are preferred over basal insulin because they have equal or superior A1C lowering efficacy and lead to weight loss instead of weight gain with a low risk of hypoglycemia. Basal insulin can be initiated if additional glucose lowering is needed after the GLP-1 RA dose has been maximized.
- 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 (ie, 80–130 mg/dL [4.4-7.2 mmol/L] for patients targeting an A1C <7% [53 mmol/mol Hb]). If the A1C target is not reached by maximally titrating basal insulin, PPG levels are likely elevated and a GLP1-RA or SGLT-2 inhibitor should be considered if the patient is not already taking one. Prandial insulin is also an option, starting with 4 units or 10% of the basal dose with the largest meal of the day. If the A1C is <8% (64 mmol/mol Hb), the basal insulin dose can be decreased by the same amount to avoid hypoglycemia. Titrate the dose over time to achieve target PPG levels <180 mg/dL (10 mmol/L). A second or third injection can be added to the other meals if needed.

- Reevaluate the appropriateness of oral medications when injectable agents are started:
  - ✔ GLP-1 RAs can be used in combination with all oral agents except DPP-4 inhibitors.
  - ✔ Continue metformin when insulin is started. Stop TZDs and sulfonylureas or reduce the dose.
  - ✔ SGLT-2 inhibitors can be continued, but educate the patient about the risk of DKA.

Treatment of Hyperglycemia in Type 1 Diabetes

- All patients with type 1 DM require exogenous insulin. Achieving adequate glycemic control usually requires intensive insulin regimens designed to provide insulin in a manner that mimics normal physiologic insulin secretion, with consistent secretion of 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 ingestion of carbohydrates (ie, prandial insulin).
- Intensive insulin regimens can be given with either multiple daily injections (MDI) or use of continuous subcutaneous insulin infusion (CSII) via an insulin pump (**Fig. 19-1**).
- A common MDI approach is one injection of long-acting insulin (eg, insulin glargine U-100) for the basal component and three injections of rapid-acting insulin (eg, insulin lispro U-100) for the prandial component (**Fig. 19-1A**). 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) (**Fig. 19-1B**). However, the ADA Standards of Care recommend that most patients should use rapid-acting insulins rather than regular insulin to reduce the risk of hypoglycemia.
- Insulin pump therapy or CSII infuses rapid-acting insulin to cover both the basal and prandial insulin needs (**Fig. 19-1C**). 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 greater flexibility and fine-tune tailoring.
- The starting insulin dose for someone with newly diagnosed type 1 DM is typically 0.4–1 units/kg/day of total insulin. The total daily insulin dose is then divided to give 50% as basal insulin and 50% as prandial insulin (distributed across meals). For example, an 80-kg patient started on 0.5 units/kg/day would start with a total daily dose of 40 units, with 20 units given as a long-acting insulin (eg, insulin detemir, glargine) and 7 units of rapid-acting insulin (eg, insulin aspart, lispro, or glulisine) with breakfast, lunch, and dinner. The insulin doses would then be adjusted based on SMBG data.
- Ideally, patients should learn to count carbohydrates so they can match their prandial insulin doses to their carbohydrate intake. Patients should also SMBG before each meal or use continuous glucose monitoring (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); refer to the textbook chapter for more detailed information.
- Pramlintide is indicated as adjunctive treatment in patients with type 1 DM who are not achieving glycemic targets despite optimization of mealtime insulin (refer to discussion earlier in this chapter). Pramlintide may improve glycemic control and minimize weight gain caused by insulin, but its use is limited by adverse effects such as nausea and vomiting, modest glucose improvements, increased injections and cost, and increased risk of hypoglycemia.
- Assess patients every 3 months if uncontrolled and every 6 months if controlled. Obtain an A1C and adjust treatment as needed. Patients on intensive insulin therapy should SMBG at least four times daily, before meals and at bedtime. Patients should also test before exercise, prior to critical tasks such as driving, and if symptoms of hypoglycemia occur. SMBG is crucial during times of intercurrent illness or stresses for early detection and prevention of DKA.
- Continuous glucose monitors report interstitial glucose levels in real time, provide insight into glucose trends, and can reduce A1C and reduce glucose variability in patients with type 1 DM. Current guidelines recommend CGM in patients with type 1 DM who are not meeting glycemic goals. They are also recommended in patients with hypoglycemia unawareness to better detect and prevent hypoglycemic events.

FIGURE 19-1

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 line]), or short-acting regular insulin (dashed line). Only one formulation of short-acting insulin is used.

(C) Insulin administration by 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.

image

Hypoglycemia

- Hypoglycemia is a common complication of some diabetes medications and is associated with falls, injury, motor vehicle accidents, decreased quality of life, and increased risk of developing dementia, CV events, arrhythmias, and death.
- The severity of hypoglycemia is classified as follows:
  - ✔ *Level 1 (hypoglycemia alert value; ≤70 mg/dL [3.9 mmol/L])*: May not cause symptoms but should be treated with a fast-acting carbohydrate and may need medication dose adjustment
  - ✔ *Level 2 (clinically significant hypoglycemia; <54 mg/dL [3.0 mmol/L])*: Serious, clinically important hypoglycemia
  - ✔ *Level 3 (severe hypoglycemia)*: Associated with cognitive impairment requiring external assistance for recovery and can be life threatening
- Initial autonomic symptoms include tachycardia, palpitations, sweating, tremors, and hunger. Neuroglycopenic symptoms often occur with BG <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.
- Some patients have hypoglycemia unawareness and are unable to detect the early warning symptoms of hypoglycemia; they are at increased risk for the serious sequelae associated with severe hypoglycemia.
- SMBG and CGM can be useful in preventing hypoglycemia. Patients must be educated to understand situations that increase risk of hypoglycemia (eg, delaying meals, during or after exercising, or fasting).
- Treatment of hypoglycemia requires ingestion of carbohydrates, preferably glucose. Patients should carry a source of fast-acting glucose with them at all times and use the “rule of 15” for proper treatment:
  - ✔ First use SMBG to confirm BG <70 mg/dL (3.9 mmol/L) and then ingest 15 g of fast-acting carbohydrates such as 1/2 cup (4 oz or 125 mL) of milk, juice, or soda; 1 tablespoon of honey; hard candy; jelly beans; or glucose tablets.
  - ✔ Repeat SMBG in 15 minutes; if the BG is <70 mg/dL (3.9 mmol/L), repeat the process.
  - ✔ Once the BG is normalized, eat a snack or meal that includes complex carbohydrates and protein to prevent further hypoglycemic episodes.
- If the patient is unconscious, give IV glucose or glucagon injection. Glucagon increases glycogenolysis in the liver and may be given in any situation in which IV glucose cannot be rapidly administered. A glucagon kit should be prescribed and readily available to all patients on insulin who have a history of or high risk for severe hypoglycemia. It can take 10–15 minutes before glucose levels start to rise, and patients often vomit. Position the patient on the side with the head tilted slightly downward to avoid aspiration.

- Clinicians should monitor hypoglycemia at every visit. Ask the patient about the frequency, severity, and timing of hypoglycemic events, need for assistance by others, or the need to administer glucagon. Reevaluate the treatment regimen of patients with frequent or severe hypoglycemia to minimize future episodes.

Complications and Comorbidities

Diabetic Ketoacidosis (DKA)

- In patients with type 1 DM, DKA is usually precipitated by omitting insulin, infection, or acute illness with resultant increases in cortisol, catecholamines, glucagon, and growth hormone.
- Patients may be alert, stuporous, or comatose at presentation. Diagnostic laboratory values include hyperglycemia, anion gap acidosis, and large ketonemia or ketonuria.
- Patients have fluid deficits of several liters and significant sodium and potassium deficits. Treatment requires restoration of intravascular volume with normal saline followed by hypotonic saline to replace free water, potassium supplements, and insulin given by continuous IV infusion.
- Constant infusion of a fixed insulin dose and administration of IV glucose when the BG level decreases to <250 mg/dL (13.9 mmol/L) are preferred over titrating the insulin infusion based on the glucose level. Rapid correction of the glucose (a decrease >75–100 mg/dL/hr [4.2–5.6 mmol/L/hr]) is not recommended because it has been associated with cerebral edema, especially in children. Continue the insulin infusion until the urine ketones clear and the anion gap closes.
- Give long-acting insulin 1–3 hours before discontinuing the insulin infusion. Perform hourly bedside monitoring of glucose and frequent monitoring of potassium (every 2–4 hours).
- Treatment with bicarbonate to correct the acidosis is generally not needed and may be harmful.
- It is essential to correct the underlying situation or medical condition that precipitated DKA.
- Metabolic improvement is manifested by an increase in serum bicarbonate and pH. Because fluid administration alone reduces BG, reduced glucose values do not necessarily indicate improving metabolic status.

Hyperosmolar Hyperglycemic State (HHS)

- HHS is a potentially life-threatening acute complication of diabetes associated with very high glucose concentrations, typically >400 mg/dL (22.2 mmol/L). It usually occurs in older patients with type 2 DM or in younger patients with prolonged hyperglycemia and dehydration or significant renal insufficiency.
- The patient presentation is similar to DKA, but HHS patients usually have much higher BG, elevated serum osmolality, and little to no ketonuria or ketonemia.
- HHS typically evolves over several days to weeks, whereas DKA evolves much faster. Large ketonemia is not usually seen because residual insulin secretion suppresses lipolysis. Infection or another medical illness is the usual precipitant.
- Fluid deficits are often greater and BG levels higher—sometimes >1000 mg/dL (55.5 mmol/L)—in patients with HHS than in patients with DKA.
- BG should be lowered very gradually with hypotonic fluids and low-dose insulin infusions (1–2 units/hr).

Macrovascular Complications

- Macrovascular complications (eg, CHD, stroke) are the leading causes of death in people with diabetes.
- The ADA recommends low-dose **aspirin** therapy (75–162 mg daily) in all patients with established ASCVD. **Clopidogrel** may be used in patients allergic to aspirin. The role of antiplatelet therapy for primary CV prevention is unclear because the benefits may be offset by a higher risk of

bleeding; some practice guidelines recommend aspirin if the 10-year risk of a CV event is >20%.

- In patients with established ASCVD, use of a GLP1-RA or an SGLT-2 inhibitor should be strongly considered.
- For all patients whose blood pressure (BP) exceeds 120/80 mm Hg, the ADA recommends dietary changes, physical activity, and weight loss in overweight or obese patients. Drug therapy using agents proven to reduce CV events should be started for BP >140/90 mm Hg. A combination of two medications should be used for BP >160/100 mm Hg.
- Initiate high-intensity statin therapy in all patients with diabetes and preexisting ASCVD regardless of baseline lipid levels. In the absence of ASCVD, prescribe a moderate-intensity statin to all patients with type 1 or type 2 DM over the age of 40. In patients <40 years of age, a moderate-intensity statin may be appropriate for patients with multiple CV risk factors. A fibrate (eg, **fenofibrate**), **omega-3 fatty acid**, or **niacin** can be added for patients with marked hypertriglyceridemia.
- Peripheral arterial disease can lead to claudication, nonhealing foot ulcers, and limb amputation. Smoking cessation, statin therapy, good glycemic control, and antiplatelet therapy are important strategies. **Cilostazol** may be useful in select patients to reduce symptoms. Revascularization surgery can be considered in some situations. Perform foot examinations during each face-to-face patient encounter and a yearly monofilament test to assess for loss of protective sensation to identify high-risk patients.

Microvascular Complications

- Efforts to improve glucose control significantly reduce the risk of developing microvascular complications and slow their progression.
- *Nephropathy*: Albuminuria is a marker of renal damage and can be predictive of end-stage renal disease. The ADA recommends screening for albuminuria upon diagnosis in persons with type 2 DM. Screening with type 1 DM should begin with puberty and after 5-years' disease duration. BP control is important for preventing and slowing progression of nephropathy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can slow the progression of renal disease in patients with diabetes. Diuretics are often necessary due to volume-expanded states and are recommended second-line therapy. The ADA recommends a BP goal <140/90 mm Hg in patients with nephropathy but a lower target (eg, <130/80) if it can be achieved without undue burden or side effects. Three or more antihypertensives are often needed to reach goal BP.
- *Retinopathy*: Patients with diabetes should have routine dilated eye examinations to fully evaluate the retina. Early background retinopathy may reverse with improved glycemic control and optimal BP control. More advanced retinopathy will not fully regress with improved glycemia, and aggressive BG reductions may acutely worsen retinopathy. Laser photocoagulation has markedly improved sight preservation. Intravitreal antivascular endothelial growth factor (VEGF) therapy is also highly effective for sight preservation. **Bevacizumab** (used off-label) and **ranibizumab** are anti-VEGF monoclonal antibodies, and **aflibercept** is a VEGF decoy receptor.
- *Neuropathy*:

  ✔ Distal symmetrical peripheral neuropathy is the most common complication in patients with type 2 DM. Paresthesias, numbness, or pain are the predominant symptoms. The feet are involved far more often than the hands. Improved glycemic control is the primary treatment and may alleviate some symptoms. Pharmacologic therapy is symptomatic and includes low-dose tricyclic antidepressants (**nortriptyline** or **desipramine**), **duloxetine**, **gabapentin**, **pregabalin**, **venlafaxine**, **topical capsaicin**, and **tramadol**.

  ✔ Gastroparesis can be severe and debilitating. Improved glycemic control, discontinuation of medications that slow gastric motility, and use of **metoclopramide** or low-dose **erythromycin** may be helpful.

  ✔ Diabetic diarrhea is often nocturnal and frequently responds to a 10- to 14-day course of an antibiotic such as **doxycycline** or **metronidazole**. **Octreotide** may be useful in unresponsive cases.

  ✔ Orthostatic hypotension may require mineralocorticoids (eg, **fludrocortisone**) or adrenergic agonists (**midodrine**).

  ✔ Erectile dysfunction is common, and initial therapy should include a trial of an oral phosphodiesterase-5 inhibitor (eg, **sildenafil**, **vardenafil**, or **tadalafil**).

EVALUATION OF THERAPEUTIC OUTCOMES

- Measure A1C every 3–6 months to follow long-term glycemic control for the previous 2–3 months, even in patients who are stable on a therapeutic regimen and meeting treatment goals (**Table 19-1**).
- SMBG provides an opportunity to adjust medications, food intake, or physical activity and enables patients to detect hypoglycemia. For patients with type 1 DM, SMBG is typically performed 4–6 times per day—prior to food intake and physical activity and at bedtime. The optimal frequency of SMBG in patients with type 2 DM on oral agents is controversial.
- CGM should be considered in adults with type 1 DM who are at least 25 years of age and those younger than 25 years of age who can demonstrate adherence to its use.
- At each visit, ask patients with type 1 DM about the frequency and severity of hypoglycemia. Document any hypoglycemic episodes requiring assistance of another person, medical attention, or hospitalization and take steps to prevent future episodes.
- Screen for complications at the time of diagnosis and thereafter as follows:
  - ✔ Obtain yearly dilated eye exams in type 2 DM and an initial exam in the first 5 years in type 1 DM, then yearly.
  - ✔ Assess BP at each visit.
  - ✔ Examine the feet at each visit, including palpation of distal pulses and visual inspection for skin integrity, calluses, and deformities.
  - ✔ Screen for pedal sensory loss annually using a 10-g force monofilament.
  - ✔ Screen for albuminuria at the time of diagnosis in patients with type 2 DM and 5 years after diagnosis in type 1 DM. At least once a year, assess urinary albumin (urine albumin-to-creatinine ratio) and eGFR in all patients with type 2 DM and in patients with type 1 DM for at least 5 years.
  - ✔ Check fasting lipid panel annually if the patient is on lipid-lowering therapy.
- Administer an annual influenza vaccine and assess for administration of the pneumococcal vaccine and hepatitis B vaccine series along with management of other CV risk factors (eg, smoking).

See Chapter 91, Diabetes Mellitus, authored by Jennifer Trujillo and Stuart Haines, for a more detailed discussion of this topic.