

CHAPTER 171

Diabetes Mellitus

Diabetes mellitus (DM) is characterized by hyperglycemia and glycosuria and is an end-point of a few disease processes (Table 171.1). The most common type occurring in childhood is type 1 DM (T1D), which is caused by autoimmune destruction of the insulin-producing β cells (islets) of the pancreas, leading to permanent insulin deficiency. Type 2 DM (T2D) results from insulin resistance and relative insulin deficiency, usually in the context of exogenous obesity. The incidence of T1D and T2D in the United States is increasing. Less common types of diabetes result from genetic defects of the insulin receptor or inherited abnormalities in sensing of ambient glucose concentration by pancreatic β cells (see Table 171.1).

DEFINITION

A **diagnosis** of DM is made based on four glucose abnormalities that may need to be confirmed by repeat testing: (1) fasting serum glucose concentration of 126 mg/dL or above, (2) a random venous plasma glucose of 200 mg/dL or above with symptoms of hyperglycemia, (3) an abnormal oral glucose tolerance test (OGTT) with a 2-hour postprandial serum glucose concentration of 200 mg/dL or above, and (4) a hemoglobin A_{1c} (HbA_{1c}) of 6.5% or above.

A patient is considered to have **impaired fasting glucose** if fasting serum glucose concentration is 100–125 mg/dL or **impaired glucose tolerance** if 2-hour plasma glucose following an OGTT is 140–199 mg/dL. Sporadic hyperglycemia can occur in children, usually in the setting of an intercurrent illness. When the hyperglycemic episode is clearly related to an illness or other physiologic stress, the probability of incipient diabetes is small (<5%).

TYPE 1 DIABETES MELLITUS

Etiology

T1D results from the autoimmune destruction of insulin-producing β cells (islets) of the pancreas. In addition to the presence of diabetes susceptibility genes, an unknown

TABLE 171.1 Classification of Diabetes Mellitus in Children and Adolescents

TYPE	COMMENT
TYPE 1 (INSULIN DEPENDENT)	
Transient neonatal	Manifests immediately after birth; lasts 1–3 mo
Permanent neonatal	Other pancreatic defects possible
Classic type 1	Glycosuria, ketonuria, hyperglycemia, islet cell positive; genetic component
TYPE 2 (NON-INSULIN DEPENDENT)	
Secondary	Cystic fibrosis, hemochromatosis, drugs (L-asparaginase, tacrolimus)
Adult type (classic)	Associated with obesity, insulin resistance; genetic component
OTHER	
Gestational diabetes	Abnormal glucose tolerance during pregnancy only, which reverts to normal postpartum; increased risk for later onset of diabetes
Maturity-onset diabetes of youth	Autosomal dominant, onset before age 25 yr; not associated with obesity or autoimmunity
Mitochondrial diabetes	Single-gene mutations include hepatocyte nuclear factors 1 β , 1 α , 4 α ; glucokinase; insulin promoter factor 1 Associated with deafness and other neurologic defects, maternal transmission—mtDNA point mutations

environmental insult presumably triggers the autoimmune process. A variety of studies have produced conflicting data regarding a host of environmental factors. These include cow's milk feeding at an early age, viral infectious agents (coxsackievirus, enterovirus, cytomegalovirus, mumps, rubella), vitamin D deficiency, and perinatal factors. T1D is thought to be primarily a T-cell-mediated disease.

Antibodies to islet cell antigens may be seen months to years before the onset of β dysfunction (Fig. 171.1). These include islet cell antibodies; insulin autoantibodies; and antibodies to insulinoma-associated protein 2 (IA-2), glutamic acid decarboxylase (GAD), Zn Transporter 8 (ZnT8), among others. The risk for diabetes increases with the number of antibodies detected in the serum. In individuals with only one detectable antibody, the risk is only 10–15%, while in individuals with three or more antibodies the risk is 55–90%. When 80–90% of the β -cell mass has been destroyed, the remaining β -cell mass is insufficient to maintain euglycemia, and clinical manifestations of diabetes result (see Fig. 171.1).

Epidemiology

The annual incidence of T1D is increasing steadily with significant geographic differences. In the United States, the annual incidence is approximately 20 in 100,000. The annual incidence in children ranges from a high of 40 in 100,000 among Scandinavian populations to less than 1 in 100,000 in

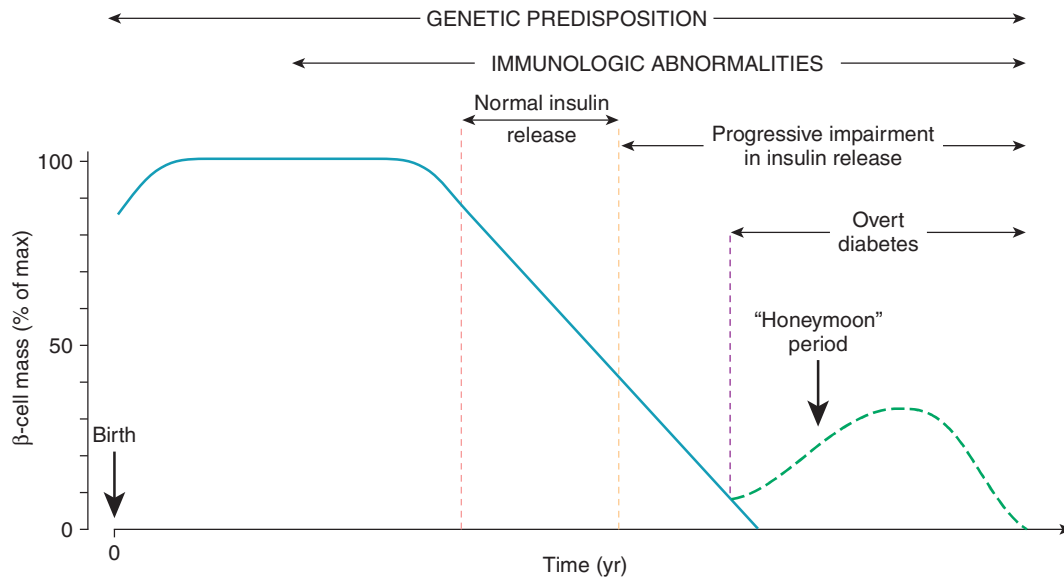


FIGURE 171.1 Schematic representation of the autoimmune evolution of diabetes in genetically predisposed individuals.

China. The prevalence of T1D in the United States is highest in non-Hispanic Whites followed by Blacks, Hispanics, and American Indians.

No overall gender difference in incidence exists. There is a peak at 4–6 years of age and a second peak at about 10–14 years of age. While genetic determinants play a role in the susceptibility to T1D, the mode of inheritance is complex and multigenic. With no family history of T1D, there is about a 0.4% risk; siblings or offspring of patients with diabetes have a risk of 2–8% for the development of diabetes; an identical twin has a 30–50% risk. The human leukocyte antigen (HLA) region on chromosome 6 provides the strongest determinant of susceptibility, accounting for approximately 40% of familial inheritance of T1D. Specific class II DR and DQ HLA alleles (HLA DR3 and HLA DR4) increase the risk of developing T1D, whereas other specific HLA alleles exert a protective effect. More than 90% of children with T1D possess HLA DR3 alleles, HLA DR4 alleles, or both. The insulin gene region variable number tandem repeat on chromosome 11 is also linked to T1D susceptibility. There is evidence for association, beyond HLA, of more than 100 other loci with T1D. Genetic factors do not fully account for susceptibility to T1D; environmental factors also play a role.

T1D is also associated with celiac disease and other autoimmune or inflammatory polyendocrinopathies such as IPEX (immune dysregulation, polyendocrinopathy, enteropathy X-linked) syndrome.

Clinical Manifestations

Hyperglycemia results when insulin secretory capacity becomes inadequate to enhance peripheral glucose uptake and to suppress hepatic and renal glucose production. Insulin deficiency usually first causes postprandial hyperglycemia and then fasting hyperglycemia. Ketogenesis is a sign of more complete insulin deficiency. Lack of suppression of gluconeogenesis and glycogenolysis further exacerbates hyperglycemia, while fatty acid oxidation generates the

ketone bodies: β -hydroxybutyrate, acetoacetate, and acetone. Protein stores in muscle and fat stores in adipose tissue are metabolized to provide substrates for gluconeogenesis and fatty acid oxidation.

The classic presentation of T1D includes polyuria, polydipsia, polyphagia, and weight loss. Glycosuria occurs when the serum glucose concentration exceeds the renal threshold for glucose reabsorption (from 160–190 mg/dL). Glycosuria causes an osmotic diuresis (including obligate loss of sodium, potassium, and other electrolytes) leading to dehydration. Polydipsia occurs as the patient attempts to compensate for the excess fluid losses. Weight loss results from the persistent catabolic state and the loss of calories through glycosuria and ketonuria.

DIABETIC KETOACIDOSIS

If the clinical features of new-onset T1D are not detected, **diabetic ketoacidosis (DKA)** will occur. DKA may also occur in patients with known T1D if insulin injections are omitted or during an intercurrent illness when greater insulin requirements are unmet in the presence of elevated concentrations of the counter-regulatory and stress hormones (glucagon, growth hormone [GH], cortisol, and catecholamines). DKA can be considered present if (1) the arterial pH is below 7.3, (2) the serum bicarbonate level is below 15 mEq/L, and (3) ketones are elevated in serum or urine.

Pathophysiology

In the absence of adequate insulin secretion, persistent partial hepatic oxidation of fatty acids to ketone bodies occurs. Two of these three ketone bodies are organic acids and lead to metabolic acidosis with an elevated anion gap. Lactic acid may contribute to the acidosis when severe dehydration results in decreased tissue perfusion. Hyperglycemia causes an osmotic diuresis that is initially compensated for by increased fluid intake. As the hyperglycemia and diuresis worsen, most patients are unable to maintain the large fluid

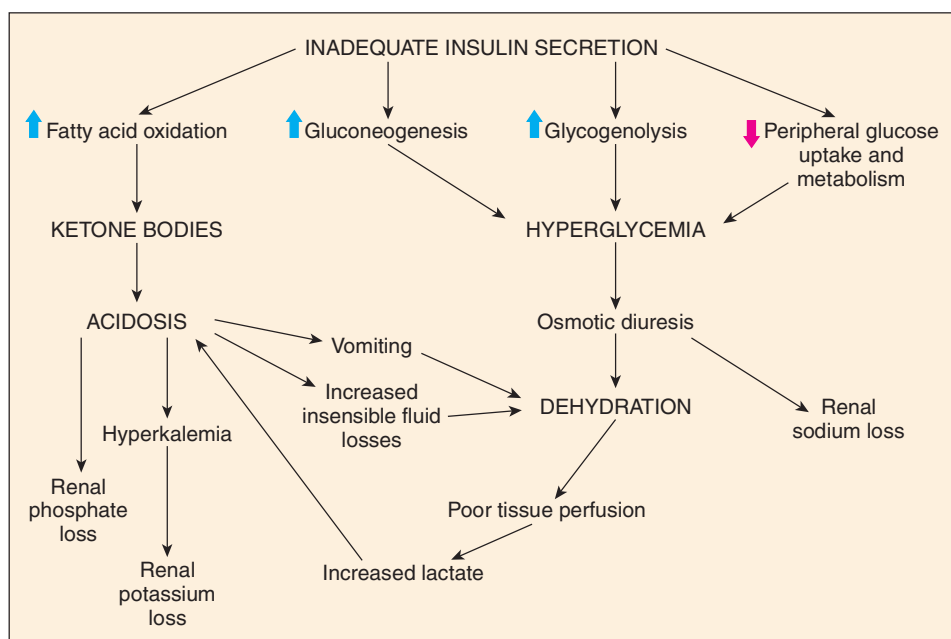


FIGURE 171.2 Pathophysiology of diabetic ketoacidosis.

intake and thus dehydration occurs. Vomiting and increased insensible water losses caused by tachypnea can worsen the dehydration. Electrolyte abnormalities occur through a loss of electrolytes in the urine and transmembrane alterations resulting from acidosis. As hydrogen ions accumulate as a result of ketoacidosis, intracellular potassium is exchanged for hydrogen ions. Serum concentrations of potassium increase initially with acidosis then decrease as serum potassium is cleared by the kidney. Depending on the duration of ketoacidosis, serum potassium concentrations at diagnosis may be increased, normal, or decreased, but intracellular potassium concentrations are depleted. A decreased serum potassium concentration is an ominous sign of total body potassium depletion. Phosphate depletion also can occur as a result of the increased renal phosphate excretion required for elimination of excess hydrogen ions. Sodium depletion is also common in ketoacidosis resulting from renal losses of sodium caused by osmotic diuresis and from gastrointestinal losses from vomiting (Fig. 171.2).

Clinical Presentation

Patients with DKA present initially with polyuria, polydipsia, nausea, and vomiting. Abdominal pain occurs frequently and can mimic an acute abdomen. The abdomen may be tender from vomiting or distended secondary to a paralytic ileus. The presence of polyuria, despite a state of clinical dehydration, indicates osmotic diuresis and differentiates patients with DKA from patients with gastroenteritis or other gastrointestinal disorders. Respiratory compensation for acidosis results in tachypnea with deep (**Kussmaul**) respirations. The *fruity* odor of acetone frequently can be detected on the patient's breath. An altered mental status can occur, ranging from disorientation to coma.

Laboratory studies reveal hyperglycemia (serum glucose concentrations ranging from 200 mg/dL to >1,000 mg/dL).

Arterial pH is below 7.30, and serum bicarbonate concentration is less than 15 mEq/L. Serum sodium concentrations may be elevated, normal, or low, depending on the balance of sodium and free water losses. The measured serum sodium concentration is artificially low, however, because of hyperglycemia. The corrected Na can be calculated using the equation: $\text{Corrected Na} = \text{measured Na} + [1.6(\text{glucose} - 100)/100]$. Hyperlipidemia also contributes to the decrease in measured serum sodium. The level of blood urea nitrogen (BUN) can be elevated with prerenal azotemia secondary to dehydration. The white blood cell count is usually elevated and can be left-shifted without implying the presence of infection. Fever is unusual and should prompt a search for infectious sources that may have triggered the episode of DKA.

Treatment

Therapy for patients with DKA involves careful replacement of fluid deficits, correction of acidosis and hyperglycemia via insulin administration, correction of electrolyte imbalances, and monitoring for complications of treatment. The optimal approach to management of DKA must strike a balance between adequate correction of fluid losses and avoidance of rapid shifts in osmolality and fluid balance. The most serious complication of DKA and its treatment is **cerebral edema** and cerebral herniation.

A patient with severe DKA is assumed to be approximately 10% dehydrated. If a recent weight measurement is available, the precise extent of dehydration can be calculated. An initial intravenous (IV) fluid bolus of a glucose-free isotonic solution (normal saline, lactated Ringer solution) at 10–20 mL/kg should be given to restore intravascular volume and renal perfusion. The remaining fluid deficit after the initial bolus should be added to maintenance fluid requirements; the total should be replaced slowly over 36–48 hours. Ongoing losses resulting

from osmotic diuresis usually do not need to be replaced unless urine output is large or signs of poor perfusion are present. Osmotic diuresis is usually minimal when the serum glucose concentration decreases to less than 300 mg/dL. To avoid rapid shifts in serum osmolality, 0.9% sodium chloride can be used as the replacement fluid for the initial 4–6 hours, followed by 0.45% sodium chloride.

Hyperglycemia

Fast-acting soluble insulin should be administered as a continuous IV infusion (0.1 U/kg/hr). Serum glucose concentrations should decrease at a rate no faster than 100 mg/dL/hr. When serum glucose concentrations decrease to less than 250–300 mg/dL, glucose should be added to the IV fluids. If serum glucose concentrations decrease to less than 200 mg/dL before correction of acidosis, the glucose concentration of the IV fluids should be increased, but the insulin infusion should not be decreased by more than half, and it should never be discontinued before resolution of acidosis.

Acidosis

Insulin therapy decreases the production of free fatty acids and protein catabolism and enhances glucose usage in target tissues. These processes correct acidosis. Bicarbonate therapy should be avoided. Potential adverse effects of bicarbonate administration include paradoxical increases in central nervous system (CNS) acidosis caused by increased diffusion of carbon dioxide across the blood-brain barrier, potential tissue hypoxia caused by shifts in the oxyhemoglobin dissociation curve, abrupt osmotic changes, and increased risk of the development of cerebral edema.

As acidosis is corrected, urine ketone concentrations may appear to rise. β -hydroxybutyrate, which is not detected in urine ketone assays, is converted with treatment to what the assay most detects, acetoacetate. Hence, minute-to-minute urine ketone concentrations are not a required index of the adequacy of therapy.

Electrolyte Imbalances

Regardless of the serum potassium concentration at presentation, total body potassium depletion is likely. Serum potassium concentrations can decrease rapidly as insulin, and then glucose therapy improves acidosis, and potassium is exchanged for intracellular hydrogen ions. When adequate urine output is shown, potassium should be added to the IV fluids. Potassium replacement should be given as 50% potassium chloride and 50% potassium phosphate at a concentration of 20–40 mEq/L. This combination provides phosphate for replacement of deficits, but avoids excess phosphate administration, which may precipitate hypocalcemia. If the serum potassium level is greater than 6 mEq/L, potassium should not be added to IV fluids until the potassium level decreases.

Monitoring

Initial laboratory measurements should include serum glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, phosphate, and magnesium concentrations; arterial or venous pH; and a urinalysis. Serum glucose measurement should be repeated every hour during therapy, and electrolyte concentrations should be repeated every 2–3 hours. Calcium, phosphate, and magnesium concentrations should be measured every 4–6 hours during therapy. Neurologic

and mental status should be assessed at frequent intervals. Any complaints of headache or deterioration of mental status should prompt rapid evaluation for possible **cerebral edema**. Symptoms indicative of possible cerebral edema include a decreased sensorium, sudden severe headache, vomiting, change in vital signs (bradycardia, hypertension, apnea), a dilated pupil, ophthalmoplegia, or seizure.

Complications

Clinically apparent **cerebral edema** occurs in 1–5% of cases of DKA. Cerebral edema is the most serious complication of DKA, with a significant mortality rate. The pathogenesis of cerebral edema likely involves osmolar shift resulting in fluid accumulation in the intracellular compartment and neuronal cell swelling. Subclinical cerebral edema is common in children with DKA, although the factors that exacerbate this process leading to symptomatic brain swelling and possible cerebral herniation are not clearly defined. Cerebral edema typically occurs 6–12 hours after therapy for DKA is begun, often following a period of apparent clinical improvement. Factors that correlate with increased risk for cerebral edema include higher initial BUN concentration, lower initial PCO_2 , failure of the serum sodium concentration to increase as glucose concentration decreases during treatment, and treatment with bicarbonate.

Signs of advanced cerebral edema include obtundation, papilledema, pupillary dilation or inequality, hypertension, bradycardia, and apnea. **Treatment** involves the rapid use of IV mannitol, endotracheal intubation, and ventilation and may require the use of a subdural bolt. Other complications of DKA are intracranial thrombosis or infarction, acute kidney injury with acute renal failure caused by severe dehydration, pancreatitis, arrhythmias caused by electrolyte abnormalities, pulmonary edema, and bowel ischemia. Peripheral edema occurs commonly 24–48 hours after therapy is initiated and may be related to residual elevations in antidiuretic hormone and aldosterone.

Transition to Outpatient Management

When the acidosis has been corrected and the patient tolerates oral feedings, the IV insulin infusion can be discontinued, and a regimen of subcutaneous (SC) insulin injections can be initiated. The first SC insulin dose should be given 30–45 minutes before discontinuation of the IV insulin infusion. Further adjustment of the insulin dose should be made over the following 2–3 days. A patient already diagnosed with T1D may be restarted on the prior doses if they were adequate. For a patient with new-onset T1D, typical starting total daily doses are approximately 0.5–0.7 U/kg per 24 hours for prepubertal patients and approximately 0.7–1 U/kg per 24 hours for adolescents, using any number of the available insulin combinations. The best and most common choice for making the transition to SC insulin is to begin by giving injections of fast-acting (bolus) insulin (lispro, aspart, or glulisine insulin) with each meal and long-acting (basal) insulin (glargine, detemir, or degludec) at bedtime. This regimen of multiple daily injections provides the most flexibility but requires the patient to administer many injections per day and to count carbohydrates in food. An alternative is a fixed mixed split dosing regimen (neutral protamine Hagedorn [NPH] and fast-acting insulin) with two daily injections.

Externally worn pumps that provide a continuous SC infusion of fast-acting insulin are available, although not usually used at the very onset of T1D. Insulin pumps provide fast-acting insulin in small basal amounts continuously every hour and will provide bolus insulin when instructed. Insulin pumps may be used by all age groups who are highly motivated to achieve tight control. The absence of SC depot insulin (glargine or detemir) (if medication runs out or the pump stops) can increase the risk of DKA.

Serum glucose concentrations should be assessed before each meal, at bedtime, and periodically at 2–3 A.M. to provide information for adjustment of the regimen. Patients and their families should begin learning the principles of diabetes care as soon as possible. Demonstration of the ability to administer insulin injections and test glucose concentrations using a glucose meter is necessary before discharge, as is knowledge of hypoglycemia management. Meal planning is crucial to control glucose in T1D. Nutrition services must be part of the care delivered to the families from diagnosis.

Honeymoon Period

In some patients with new onset of T1D, the β -cell mass has not been completely destroyed. The remaining functional β cells seem to recover function with insulin treatment. When this occurs, exogenous insulin requirements decrease. This is a period of stable blood glucose control, often with nearly normal glucose concentrations. This phase of the disease, known as the honeymoon period, usually starts in the first weeks of therapy, often continues for 3–6 months, and can last 2 years.

Outpatient Type 1 Diabetes Mellitus Management

Management of T1D in children requires a comprehensive approach with attention to medical, nutritional, and psychosocial issues. Therapeutic strategies should be flexible with the individual needs of each patient and the family taken into account. Optimal care involves a team of diabetes professionals, including a physician, a diabetes nurse educator, a dietitian, and a social worker or psychologist.

Goals

The Diabetes Control and Complications Trial established that intensive insulin therapy, with the goal of maintaining blood glucose concentrations as close to normal as possible, can delay the onset and slow the progression of complications of diabetes (retinopathy, nephropathy, neuropathy). Attaining this goal using intensive insulin therapy can increase the risk of hypoglycemia. The adverse effects of hypoglycemia in young children may be significant because the immature CNS may be more susceptible to hypoglycemia. Although the risk for diabetic complications increases with duration of diabetes, there is controversy as to whether the increase of risk is lower in the prepubertal years than in adolescence and adulthood.

Given the benefits of stable, near normal blood glucose concentrations, a goal of HbA_{1c} below 7.5% is set for children of all ages. Preprandial blood glucose target concentrations are 90–130 mg/dL and concentrations before bedtime and overnight of 90–150 mg/dL. Goals of therapy need to take into account other individual characteristics, such as a past history of severe hypoglycemia and the abilities of the patient and family.

Insulin Regimens

Many types of insulin differ in duration of action and time to peak effect (Table 171.2). These insulins can be used in various combinations, depending on the needs and goals of the individual patient. The most commonly used regimen is that of multiple injections of fast-acting insulin given with meals in combination with long-acting basal insulin given at bedtime. This regimen provides flexibility but requires administration of many injections per day and will require assistance for young children. After the total daily dose of insulin is determined, 30–50% is given as long-acting insulin, and the remainder is given as fast-acting insulin, divided according to the need for corrections of high glucose levels and for meals. To correct for hyperglycemia, one can determine the insulin sensitivity using the 1,800/1,500 rule: dividing 1,800 (or 1,500) by the total daily dose of insulin to determine how many milligrams per deciliter of glucose will decrease with one unit of insulin. The insulin:carbohydrate ratio is used to calculate insulin for the

TABLE 171.2 Representative Profiles of Insulin

INSULIN	ONSET	PEAK ACTION	DURATION
VERY SHORT ACTING			
Lispro, aspart, glulisine	5–15 min	30–90 min	3–5 hr
SHORT ACTING			
Regular	30–60 min	2–3 hr	5–8 hr
INTERMEDIATE ACTING			
Neutral protamine Hagedorn (NPH) (isophane)	2–4 hr	4–10 hr	10–16 hr
LONG ACTING			
Glargine	2–4 hr	None	20–24 hr
Detemir	2–4 hr	6–14 hr	16–20 hr
Degludec	2–4 hr	None	24+ hr

Data from Wolfsdorf JL, ed. Intensive Diabetes Management. 4th ed. Alexandria, VA: American Diabetes Associations; 2009.

carbohydrate content of food; 500 divided by the total daily dose determines the number of grams of carbohydrate that requires one unit of insulin.

Lispro, aspart, and glulisine insulin are synthetic human insulin analogs in which amino acid alterations result in fast absorption and onset of action (see Table 171.2). Because of the short duration of action, these are used in combination with long-acting insulin. Glargine and detemir are insulin analogs with increased solubility at acidic pH and decreased solubility at physiologic pH. They have a duration of greater than 24 hours and act as a basal insulin.

Newly diagnosed patients in the honeymoon period may require 0.4–0.6 U/kg per 24 hours. Prepubertal patients with diabetes longer than 1–2 years typically require 0.5–1 U/kg per 24 hours. During middle adolescence when elevated GH concentrations produce relative insulin resistance, insulin requirements increase by 40–50%, and doses of 1–2 U/kg per 24 hours are typical.

Blood Glucose Testing

Blood glucose should be routinely monitored before each meal and at bedtime. Hypoglycemia during the night or excessive variability in the morning glucose concentrations should prompt additional testing at 2 or 3 A.M. to ensure that there is no consistent hypoglycemia or hyperglycemia. During periods of illness or when blood glucose concentrations are higher than 300 mg/dL, urine ketones also should be tested. Continuous glucose monitors (CGM), which provide minute-to-minute blood glucose concentration information, can be useful in following trends of blood glucose concentrations and have been approved to replace fingerstick blood glucose testing.

Insulin Pumps, Continuous Glucose Monitors, and Closed-Loop Systems

Insulin pumps that provide a continuous SC infusion of short-acting insulin also are available and are being used by children and adolescents who are highly motivated to achieve tight control. Sensor augmented insulin pump therapy refers to the use of an insulin pump in conjunction with a CGM. Data from a CGM is used to manually adjust the insulin pump settings. Sensor augmented insulin pump therapy with threshold suspend refers to the use of an insulin pump and CGM system that will either detect or predict low blood glucose (BG) and suspend insulin pump until normoglycemia is achieved. Hybrid closed-loop system refers to the recent advent of an insulin pump and CGM system that automatically increases, decreases, or suspends basal rates in response to glucose levels. One such system will also give additional bolus insulin based on rate of rise of BG value and elevation of BG level. These closed-loop systems are preparing the way for a fully automated closed loop.

Nutrition

Balancing the daily meal plan with the dosages of insulin is crucial for maintaining serum glucose concentrations within the target range and avoiding hypoglycemia or hyperglycemia. The content and schedule of meals vary according to the type of insulin regimen used. It is recommended that carbohydrates contribute 50–65% of the total calories, protein 12–20%, and fat less than 30%. Saturated fat should contribute

less than 10% of the total caloric intake, and cholesterol intake should be less than 300 mg per 24 hours. High-fiber content is recommended.

Patients using multiple daily injections or the insulin pump can maintain a more flexible meal schedule with regard to the timing of meals and the carbohydrate content. These patients give an injection of insulin before or immediately after each meal with the total dose calculated according to the carbohydrate content of the meal. Further adjustments in the dose can be made based on the measured serum glucose concentration and plans for activity during the day. Children using a twice-a-day combination of intermediate-acting and fast-acting insulins need to maintain a relatively consistent meal schedule so that carbohydrate absorption and insulin action peaks correspond. A typical meal schedule for a patient using this type of regimen involves three meals and three snacks daily. The total carbohydrate content of the meals and snacks should be kept constant.

Long-Term Glycemic Control

Measurements of **glycohemoglobin** or **HbA_{1c}** reflect the average blood glucose concentration over the preceding 3 months and provide a means for assessing long-term glycemic control. HbA_{1c} should be measured four times a year, and the results should be used for counseling of patients. The American Diabetes Association has set HbA_{1c} targets for children at less than 7.5%. Measurements of HbA_{1c} are inaccurate in patients with hemoglobinopathies. Glycosylated albumin or fructosamine can be used in these cases.

Complications

Patients with T1D for more than 3–5 years should receive an annual ophthalmologic examination for retinopathy. Urine should be collected annually for assessment of microalbuminuria, which suggests early renal dysfunction and indicates a high risk of progression to nephropathy. Treatment with angiotensin-converting enzyme inhibitors may halt the progression of microalbuminuria. In children with T1D, annual cholesterol measurements and periodic assessment of blood pressure are recommended. Early detection of hypertension and hypercholesterolemia with appropriate intervention can help limit future risk of coronary disease.

Other Disorders

Chronic autoimmune lymphocytic thyroiditis is particularly common and can result in hypothyroidism. Because symptoms can be subtle, thyroid function tests should be performed annually. Other disorders that occur with increased frequency in children with T1D include celiac disease, immunoglobulin A deficiency, Addison disease, and peptic ulcer disease.

Special Problems: Hypoglycemia

Hypoglycemia occurs commonly in patients with T1D. For patients in adequate or better control, it is expected to occur on average once or twice a week. Severe episodes of hypoglycemia, resulting in seizures or coma or requiring assistance from another person, occur in 10–25% of these patients per year.

Hypoglycemia in patients with T1D results from a relative excess of insulin in relation to the serum glucose concentration. This excess can be caused by alterations in the dose, timing, or absorption of insulin; alterations of carbohydrate intake; or changes in insulin sensitivity resulting from activity. Defective counter-regulatory responses also contribute to hypoglycemia. Abnormal glucagon responses to falling serum glucose concentrations develop within the first few years of the disease, and abnormalities in epinephrine release occur after a longer duration.

Lack of awareness of hypoglycemia occurs in approximately 25% of patients with diabetes. Recent episodes of hypoglycemia may play a role in the pathophysiology of *hypoglycemia unawareness*; after an episode of hypoglycemia, autonomic responses to subsequent episodes are reduced. A return of symptoms of hypoglycemia can be exhibited in these patients after 2–3 weeks of strict avoidance of hypoglycemic episodes.

Symptoms of hypoglycemia include those resulting from neuroglycopenia (headache, visual changes, confusion, irritability, or seizures) and those resulting from the catecholamine response (tremors, tachycardia, diaphoresis, or anxiety). Mild episodes can be treated with administration of rapidly absorbed oral glucose (glucose gel or tablets or fruit juices). More severe episodes that result in seizures or loss of consciousness at home should be treated with glucagon, which can be given as an injection or intranasal. IV glucose should be given in hospital settings.

Prognosis

Long-term complications of T1D include retinopathy, nephropathy, neuropathy, and macrovascular disease. Evidence of organ damage caused by hyperglycemia is rare in patients with diabetes of less than 5–10 years duration; clinically apparent disease rarely occurs before 10–15 years duration. Diabetic retinopathy is the leading cause of adult blindness in the United States. Nephropathy eventually occurs in 30–40% and accounts for approximately 30% of all new adult cases of end-stage renal disease. Neuropathy occurs in 30–40% of postpubertal patients with T1D and leads to sensory, motor, or autonomic deficits. Macrovascular disease results in an increased risk of myocardial infarction and stroke among individuals with diabetes.

Intensive control of diabetes, using frequent blood glucose testing, continuous glucose monitoring, and multiple daily injections of insulin or an insulin pump, can reduce the development or progression of diabetic complications, including a 76% reduction of risk for retinopathy, a 39% reduction in microalbuminuria, and a 60% reduction in clinical neuropathy. For pubertal and adult patients, the benefits of intensive therapy likely outweigh the increased risk for hypoglycemia. For younger patients, in whom the risks for hypoglycemia are greater and the benefits of tight glucose control may be lower, a less intensive regimen may be appropriate.

TYPE 2 DIABETES MELLITUS

Pathophysiology

T2D can occur as the result of various pathophysiologic processes; however, the most common form results from

peripheral insulin resistance and compensatory hyperinsulinemia, followed by failure of the pancreas to maintain adequate insulin secretion (see Table 171.1).

Epidemiology

The prevalence of T2D in children is increasing in parallel with childhood obesity and is highest in children of ethnic groups with a high prevalence of T2D in adults, including those of Native, Hispanic, and African descent. Obesity, metabolic syndrome, ethnicity, and a family history of T2D are risk factors. Autoantibodies to the pancreas are present among some clinically assumed to have T2D, compounding the difficulty in differentiating T1D from T2D at the time of diagnosis.

Clinical Manifestations and Differential Diagnosis

Fasting and postprandial glucose levels for diagnosis of T2D are the same as those for T1D. The diagnosis of T2D may be suspected on the basis of polyuria and polydipsia in a background of the metabolic syndrome. Differentiating T2D from T1D in children on clinical grounds alone can be challenging. The possibility of T2D should be considered in patients who are obese, have a strong family history of T2D, have other characteristics of the metabolic syndrome, or have absence of antibodies to β -cell antigens at the time of diagnosis of diabetes. **Acanthosis nigricans**, a dermatologic manifestation of hyperinsulinism and insulin resistance, presents as hyperkeratotic pigmentation in the nape of the neck and in flexural areas and is noted as a sign in the metabolic syndrome (Fig. 171.3). Although ketoacidosis occurs far more commonly in T1D, it also can occur in patients with T2D under conditions of physiologic stress and cannot be used as an absolute differentiating factor. T2D can be confirmed by the evaluation of insulin or C-peptide responses to stimulation with oral carbohydrate and in the absence of islet cell autoreactivity.

Therapy

T2D is the result of a combination of insulin resistance, relative insulin deficiency, and a secretory β -cell defect. Asymptomatic patients with mildly elevated glucose values (slightly >126 mg/dL for fasting or slightly >200 mg/dL for random glucose) may be managed initially with lifestyle modifications, including nutrition therapy (dietary adjustments) and increased exercise, which has been shown to decrease insulin resistance. In most children with new-onset, uncomplicated T2D, oral agents are usually the first line of therapy. Metformin, an insulin secretagogue, and liraglutide, a GLP-1 analog, are approved by the U.S. Food and Drug Administration for use in children. Metformin carries the rare side effect of lactic acidosis, occurring mainly in patients with compromised renal function. The most common side effect of metformin is gastrointestinal upset. Liraglutide is typically added if monotherapy with metformin fails. If ketonuria or ketoacidosis occur, insulin treatment is necessary to first achieve adequate glycemic control but may be discontinued within weeks with continuation of oral medications. Insulin therapy may be added if monotherapy with metformin fails.



FIGURE 171.3 Acanthosis nigricans. Velvety hyperpigmentation involves the axillae in this patient. From Paller AS, Mancini AJ. *Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence*. 5th ed. Elsevier; 2016 [fig. 23–26].

Because T2D may have a long preclinical course, early diagnosis is possible in subjects at risk who have the **metabolic syndrome**. Significant lifestyle modifications, such as improved eating habits and increased exercise, have a role in preventing or decreasing the morbidity of T2D. Finally, it is critical to monitor and manage the other components of metabolic syndrome, such as advanced pubertal development, hypertension, hyperlipidemia, and polycystic ovary syndrome in females.

MATURITY-ONSET DIABETES OF YOUTH (MODY)

MODY comprises a group of monogenetic dominantly inherited forms of relatively mild diabetes with onset before age 25 years. Insulin resistance does not occur in these patients; instead, the primary abnormality is an insufficient insulin secretory response to glycemic stimulation. There are multiple forms, but the most common forms are due to mutations in HNF1 α , HNF4 α , HNF1 β , and glucokinase genes. Treatment depends on the type and can include the use of sulfonylureas.

PEARLS FOR PRACTITIONERS

See *Endocrinology: Pearls for Practitioners* at the end of this section.