DIABETES MELLITUS

Perspective

Diabetes mellitus is the most common endocrine disease. It comprises a heterogeneous group of hyperglycemic disorders characterized by high serum glucose concentration and disturbances of carbohydrate and lipid metabolism. Acute complications include hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS). Long-term complications affect multiple organ systems through involvement of the microvasculature and include retinopathy, nephropathy, neuropathy, and angiopathy. As a result, complications such as coronary and cerebral vascular disease, blindness, chronic kidney disease, complicated infections, and amputations are present in a much higher incidence in diabetics than in nondiabetics. Diabetes is frequently ranked as one of the five major chronic diseases that account for a significant proportion of our health care spending. Several trials have shown to varying degrees that tight glucose control can reduce risk of death and several microvascular complications. Patients with diabetes mellitus incur emergency department (ED) costs three times higher than those of nondiabetic patients and are admitted to the hospital four times more often.

Principles of Disease

Normal Physiology

Maintenance of the plasma glucose concentration is critical to survival because plasma glucose is the predominant metabolic fuel used by the central nervous system (CNS). The CNS cannot synthesize glucose, store more than a few minutes' supply, or concentrate glucose from the circulation. Brief hypoglycemia can cause profound CNS dysfunction, and prolonged severe hypoglycemia may cause cellular death. Glucose regulatory systems have evolved to prevent or to correct hypoglycemia.

The plasma glucose concentration is normally maintained within a relatively narrow range, between 60 and 150 mg/dL, despite wide variations in glucose levels after meals and exercise. Glucose is derived from three sources: intestinal absorption from the diet; glycogenolysis, the breakdown of glycogen; and gluconeogenesis, the formation of glucose from precursors, including lactate, pyruvate, amino acids, and glycerol. After glucose ingestion, the plasma glucose concentration increases as a result of glucose absorption. Endogenous glucose production is suppressed. Plasma glucose then rapidly declines to a level below the baseline.

Insulin. Insulin receptors on the beta cells of the pancreas sense elevations in blood glucose concentration and trigger insulin release into the blood. For incompletely understood reasons, glucose taken by mouth evokes more insulin release than parenteral glucose does. Certain amino acids induce insulin release and even cause hypoglycemia in some patients. Sulfonylurea oral hypoglycemic agents work, in part, by stimulating the release of insulin from the pancreas.

The number of receptor sites helps determine the sensitivity of the particular tissue to circulating insulin. The number and sensitivity of receptor sites are also the primary factors in the long-term efficacy of the sulfonylurea oral hypoglycemic agents. Receptor sites are increased in glucocorticoid deficiency and may be relatively decreased in obese patients.

Under normal circumstances, insulin is rapidly degraded through the liver and kidneys. The half-life of insulin is 3 to 10 minutes in the circulation. Whereas insulin is the major anabolic hormone pertinent to the diabetic disorder, glucagon plays the role of the major catabolic hormone in disordered glucose homeostasis.

Although most tissues have the enzyme systems required to synthesize and to hydrolyze glycogen, only the liver and kidneys contain glucose-6-phosphatase, the enzyme necessary for the release of glucose into the circulation. The liver is essentially the sole source of endogenous glucose production. Renal gluconeogenesis and glucose release contribute substantially to the systemic glucose pool only during prolonged starvation.

The hepatocyte does not require insulin for glucose to cross the cell membrane. However, insulin augments both the hepatic glucose uptake and storage needed for the process of energy generation and glycogen and fat synthesis. Insulin inhibits hepatic gluconeogenesis and glycogenolysis.

Muscle can store and use glucose, primarily through glycolysis to pyruvate, which is reduced to lactate or transaminated to form alanine. Lactate released from muscle is transported to the liver, where it serves as a gluconeogenic precursor. Alanine may also flow from muscle to liver. During fasting, muscle can reduce its glucose uptake, oxidize fatty acids for its energy needs, and, through proteolysis, mobilize amino acids for transport to the liver as gluconeogenic precursors. Adipose tissue can also use glucose for fatty acid synthesis for oxidation to form triglycerides. During fasting, adipocytes can also decrease their glucose use and satisfy energy needs through the beta oxidation of fatty acids. Other tissues do not have the capacity to decrease glucose use on fasting and therefore produce lactate at relatively fixed rates.

Glucose transport across the fat cell membrane also requires insulin. A large percentage of the adipocyte glucose is metabolized to form α-glycerophosphate, required for the esterification of fatty acids to form triglycerides. Although most insulin-mediated fatty acid synthesis occurs in the liver, a very small percentage occurs...
in fat cells, with use of the acetyl coenzyme A generated by glucose metabolism. Very low levels of insulin are required to inhibit intracellular lipolysis while stimulating the extracellular lipolysis required for circulating lipids to enter the fat cell.

Glucose Regulatory Mechanisms. Maintenance of the normal plasma glucose concentration requires precise matching of glucose use and endogenous glucose production or dietary glucose delivery. The regulatory mechanisms that maintain systemic glucose balance involve hormonal, neurohumoral, and autoregulatory factors. Glucose regulatory hormones include insulin, glucagon, epinephrine, cortisol, and growth hormone. Insulin is the main glucose-lowering hormone. Insulin suppresses endogenous glucose production and stimulates glucose use. Insulin is secreted from the beta cells of the pancreatic islets into the hepatic portal circulation and has important actions on the liver and the peripheral tissues. Insulin stimulates glucose uptake, storage, and use by other insulin-sensitive tissues, such as fat and muscle.

Counter-regulatory hormones include glucagon, epinephrine, norepinephrine, growth hormone, and cortisol. When glucose is not transported into the cells because of either a lack of food intake or a lack of insulin, the body perceives a “fasting state” and releases glucagon, attempting to provide the glucose necessary for brain function. In contrast to the fed state, in the fasting state the body metabolizes protein and fat. Glucagon is secreted from the alpha cells of the pancreatic islets into the hepatic portal circulation. Glucagon lowers hepatic levels of fructose 2,6-bisphosphate, resulting in decreased glycolysis and increased gluconeogenesis, an effect that may be enhanced by ketosis. Glucagon increases the activity of adenylate cyclase in the liver, thereby increasing hepatic glycogenolysis and gluconeogenesis. Glucagon acts to increase ketone production in the liver. Thus, whereas insulin is an anabolic agent that reduces blood glucose concentration, glucagon is a catabolic agent that increases blood glucose concentration. Glucagon is released in response to hypoglycemia as well as to stress, trauma, infection, exercise, and starvation. It increases hepatic glucose production within minutes, although transiently.

Epinephrine both stimulates hepatic glucose production and limits glucose use through both direct and indirect actions mediated by both alpha-adrenergic and beta-adrenergic mechanisms. Epinephrine also acts directly to increase hepatic glycogenolysis and gluconeogenesis. It acts within minutes and produces a transient increase in glucose production but continues to support glucose production at approximately basal levels thereafter. Norepinephrine exerts hyperglycemic actions by mechanisms similar to those of epinephrine, except that norepinephrine is released from axon terminals of sympathetic postganglionic neurons.

Growth hormone initially has a plasma glucose–lowering effect. Its hypoglycemic effect does not appear for several hours. Thus, growth hormone release is not critical for rapid glucose counter-regulation; this is also true for cortisol. In the long term, both growth hormone and cortisol may also increase glucose production.

Types of Diabetes

The American Diabetes Association (ADA) defines four major types of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, and diabetes due to secondary disease processes or drugs. The 1997 National Diabetes Data Group report discontinued the use of the terms insulin-dependent diabetes mellitus and non–insulin-dependent diabetes mellitus because they are confusing and clinically inaccurate. In addition, use of Arabic numerals (1 and 2) instead of Roman numerals is the standard. The most recent update to the standards of care for diabetes was published in January 2011. The diagnostic criteria for diagnosis of diabetes were changed in 2010 from the previous standards of elevated fasting glucose concentration and abnormal result of the 2-hour oral glucose tolerance test (OGTT) to use of the hemoglobin A1c (HbA1c) value as the preferred confirmatory test. An HbA1c value above 6.5% is now considered diagnostic of diabetes. However, the fasting plasma glucose concentration and 2-hour OGTT are still considered valid, as is the presence of a random glucose measurement of more than 200 mg/dL in a nonfasting patient. In addition, the use of fasting plasma glucose concentration may help identify patients at risk for diabetes (if their glucose concentration is elevated but not crossing the threshold for diagnosis of diabetes).

Type 1 Diabetes Mellitus. Type 1 diabetes is characterized by abrupt failure of production of insulin with a tendency to ketosis even in the basal state. Parenteral insulin is required to sustain life. From 85 to 90% of patients with type 1 diabetes demonstrate evidence of one or more autoantibodies implicated in the cell-mediated autoimmune destruction of the beta cells of the pancreas. Strong human leukocyte antigen (HLA) associations are also found in type 1 diabetes. The autoimmune destruction has multiple genetic predispositions and may be related to undefined environmental insults.

Type 2 Diabetes Mellitus. Patients with type 2 diabetes may remain asymptomatic for long periods and show low, normal, or elevated levels of insulin because of insulin resistance. Ketosis is rare in type 2 disease. Patients have a high incidence of obesity. Hypertriglyceridemia is also frequently noted. No association exists with viral infections, islet cell autoantibodies, or HLA expression. Hyperinsulinemia may be related to peripheral tissue resistance to insulin because of defects in the insulin receptor. Defects in muscle glycogen synthesis have an important role in the insulin resistance that occurs in type 2.

Gestational Diabetes. Gestational diabetes “mellitus” is characterized by an abnormal OGTT result that occurs during pregnancy and either reverts to normal during the postpartum period or remains abnormal. The clinical pathogenesis is thought to be similar to that of type 2. The clinical presentation is usually nonketotic hyperglycemia during pregnancy. Screening is performed around the 24th to 28th week with a 75-g oral glucose load in a woman with no prior history of diabetes.

Diabetes due to Other Causes. Myriad other causes of diabetes have been identified; these include chronic pancreatitis, cystic fibrosis, genetic defects in the beta cell or in insulin receptors, and chemical induced (such as Vacor and chemotherapeutic, antipsychotic, or antiretroviral medications). The management of diabetes due to these conditions is cause specific and depends on whether the underlying pathophysiological process more closely resembles type 1 or type 2 diabetes.

Impaired Glucose Tolerance. Impaired glucose tolerance (IGT) and its analogue, impaired fasting glucose (IFG), are considered to identify individuals at high risk for development of diabetes. This group is composed of persons whose plasma glucose levels are between normal and diabetic and who are at increased risk for the development of diabetes and cardiovascular disease. The pathogenesis is thought to be related to insulin resistance. Presentations of IGT/IFG include nonketotic hyperglycemia, insulin resistance, hyperinsulinism, and often obesity. IGT/IFG differs from the other classes in that it is not associated with the same degree of complications of diabetes mellitus. Many of these patients even spontaneously have normal glucose tolerance. One should not be complacent about the patient with IGT because the decompensation of this group into the category of diabetes mellitus is 1 to 5% per year.

Epidemiology

The prevalence of diabetes is difficult to determine because many standards have been used. Regardless, the most recent data
estimate that 8.3% of Americans of all ages and 11.3% of all adults older than 20 years have diabetes. Approximately 215,000 Americans younger than 20 years have diabetes. Of these, 5 to 10% have type 1, and 90 to 95% have type 2; other types account for 1 to 5% of cases.

The peak age at onset of type 1 diabetes is 10 to 14 years. Approximately 1 of every 600 schoolchildren has this disease. In the United States the prevalence of type 1 is approximately 0.26% by the age of 20 years, and the lifetime prevalence approaches 0.4%. The annual incidence among persons from birth to 16 years of age in the United States is 12 to 14 per 1 million population. The incidence is age dependent, increasing from near-absence during infancy to a peak occurrence at puberty and another small peak at midlife.

The morbidity in diabetes is related primarily to its vascular complications. A mortality rate of 36.8% has been related to cardiovascular causes, 17.5% to cerebrovascular causes, 15.5% to diabetic comas, and 12.5% to renal failure.

Pathophysiology and Etiology

Type 1 diabetes results from a chronic autoimmune process that usually exists in a preclinical state for years. The classic manifestations of type 1—hyperglycemia and ketosis—occur late in the course of the disease, an overt sign of beta cell destruction. The most striking feature of long-standing type 1 diabetes is the nearly total lack of insulin-secreting beta cells and insulin, with the preservation of glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic polypeptide-secreting cells.

Although the exact cause of diabetes remains unclear, research has provided many clues. Studies of the pathogenesis of diabetes mellitus have demonstrated that the cause of the disordered glucose homeostasis varies from individual to individual. This cause may determine the presentation in each patient. Individual patients are currently not studied for the source of their disease except on an experimental basis. The goals of the work in progress, however, are to identify who is susceptible to the development of diabetes and to prevent diabetic emergencies and sequelae or to prevent expression of the disease.

A genetic basis for diabetes is suggested by the association of type 1 disease with certain HLA markers and by the findings of numerous twin and family studies. Families who move from areas with a low frequency of type 1 diabetes to areas with a high frequency have an incidence of disease similar to that in the areas where they reside; this suggests an environmental basis for diabetes. An autoimmune cause has been clearly demonstrated in many type 1 diabetic patients. Islet cell amyloid has also been associated with diabetes. In both types, a variety of viruses have been implicated, most notably congenital rubella, Coxsackievirus B, and cytomegalovirus.

Research has identified two groups of cellular carbohydrate transporters in cell membranes. Sodium-linked glucose transporters are found primarily in the intestine and kidney. The glucose transporter (GLUT) proteins are found throughout the body and transport glucose by facilitated diffusion down concentration gradients. The GLUT-4 transporter, found primarily in muscle, is insulin responsive, and a signaling defect in the protein may be responsible for insulin resistance in some diabetic patients.

Clinical Features

Type 1

The patient with type 1 diabetes is usually lean, younger than 40 years, and ketosis prone. Plasma insulin levels are absent to low; plasma glucagon levels are high but suppressible with insulin, and patients require insulin therapy when symptoms appear. Onset of symptoms may be abrupt, with polydipsia, polyuria, polyphagia, and weight loss developing rapidly. In some cases the disease is heralded by ketoacidosis. Myriad problems related to type 1 diabetes may prompt an ED visit; these include acute metabolic complications, such as DKA, and late complications, such as cardiovascular or circulatory abnormalities, retinopathy, nephropathy, neuropathy, foot ulcers, severe infections, and various skin lesions.

Type 2

The patient with type 2 diabetes is usually middle-aged or older and overweight, with normal to high insulin levels. Insulin levels are lower than would be predicted for glucose levels, however, leading to a relative insulin deficiency. All type 2 patients demonstrate impaired insulin function related to poor insulin production, failure of insulin to reach the site of action, or failure of end-organ response to insulin.

As with type 1 diabetes, research suggests that distinct subgroups of patients fall within the classification of type 2 diabetes. Although most adult patients are obese, 20% are not. Nonobese patients form a subgroup with a different disease, more similar to type 1. Younger patients with type 2 diabetes were previously thought to have a disease with a different course and risk factors, referred to as maturity-onset diabetes of the young. However, one of the fastest-rising subgroups of patients with type 2 diabetes is now young adults and children, who have a disease similar to that seen in older adults and thought to be due to the rise in obesity in this age group.

Symptoms tend to begin more gradually in type 2 diabetes than in type 1. The diagnosis of type 2 is often made by the discovery of an elevated blood glucose level on routine laboratory examination. Hyperglycemia may be controlled by dietary therapy, oral hypoglycemic agents, or insulin administration, depending on the individual. Decompensation of disease usually leads to HHS rather than to ketoacidosis.

Diagnostic Strategies

Serum Glucose

As a rule, any random plasma glucose level above 200 mg/dL, HbA1c value above 6.5%, fasting plasma glucose concentration above 126 mg/dL, or 2-hour postload OGTT is sufficient to establish the diagnosis of diabetes. In the absence of hyperglycemia with metabolic decompensation, these criteria should be confirmed by repeated testing on a different day. Confirmation can be made by the same test or two different tests (fasting plasma glucose and HbA1c, for example). A value of 150 mg/dL is likely to distinguish diabetic from nondiabetic patients more accurately. Formal OGTTs are unnecessary except during pregnancy or in patients who are thought to have diabetes but who do not meet the criteria for a particular classification. The World Health Organization and ADA provide protocols for performance of the OGTT.

Glycosylated Hemoglobin

Measurement of glycosylated hemoglobin (HbA1c) is one of the most important ways to assess the level of glucose control. Elevated serum glucose binds progressively and irreversibly to the amino-terminal valine of the hemoglobin B chain. The HbA1c measurement provides insight into the quality of glycemic control over time. Given the long half-life of red blood cells, the percentage of HbA1c is an index of glucose concentration of the preceding 6 to 8 weeks, with normal values approximately 4 to 6% of total hemoglobin, depending on the assay used. Levels in patients with poorly controlled disease may reach 10 to 12%.
Measurement of glycated albumin can be used to monitor diabetic control during 1 to 2 weeks because of its short half-life but is rarely used clinically. The ADA recommends at least biannual measurements of HbA1c for the follow-up of all types of diabetes. The ADA currently sets an HbA1c value of less than 7% as a treatment goal.

Principles of Disease

Protection against hypoglycemia is normally provided by cessation of insulin release and mobilization of counter-regulatory hormones, which increase hepatic glucose production and decrease glucose use. Diabetic patients using insulin are vulnerable to hypoglycemia because of insulin excess and failure of the counter-regulatory system.

Hypoglycemia has many causes: missing a meal (decreased intake), increased energy output (exercise), and increased insulin dosage. It can also occur in the absence of any precipitant. Oral hypoglycemic agents have also been implicated in causing hypoglycemia, both in the course of therapy and as an agent of overdose.

Hypoglycemia without warning symptoms, or hypoglycemia unawareness, is a dangerous complication of type 1 diabetes probably caused by previous exposure to low blood glucose concentrations. Even a single hypoglycemic episode can reduce neurohumoral counter-regulatory responses to subsequent episodes. Other factors associated with recurrent hypoglycemic attacks include overaggressive or intensified insulin therapy, longer history of diabetes, autonomic neuropathy, and decreased epinephrine secretion or sensitivity.

The Somogyi phenomenon is a common problem associated with iatrogenic hypoglycemia in the type 1 diabetic patient. The phenomenon is initiated by an excessive insulin dosage, which results in an unrecognized hypoglycemic episode that usually occurs in the early morning while the patient is sleeping. The counter-regulatory hormone response produces rebound hyperglycemia, evident when the patient awakens. Often, both the patient and the physician interpret this hyperglycemia as an indication to increase the insulin dosage, which exacerbates the problem. Instead, the insulin dosage should be lowered or the timing changed.

Clinical Features

Symptomatic hypoglycemia occurs in most adults at a blood glucose level of 40 to 50 mg/dL. The rate at which glucose decreases, however, and the patient’s age, gender, size, overall health, and previous hypoglycemic reactions contribute to symptom development. Signs and symptoms of hypoglycemia are caused by excessive secretion of epinephrine and CNS dysfunction and include sweating, nervousness, tremor, tachycardia, hunger, and neurologic symptoms ranging from bizarre behavior and confusion to seizures and coma. In patients with hypoglycemia unawareness, the prodrome to marked hypoglycemia may be minimal or absent. These individuals may rapidly become unarousable without warning. They may have a seizure or show focal neurologic signs, which resolve with glucose administration.

Diagnostic Strategies

The cardinal laboratory test for hypoglycemia is blood glucose concentration. It should be obtained, if possible, before therapy is begun. As noted, dipstick readings are helpful in permitting rapid, reasonably accurate blood glucose estimates before therapy.

Laboratory testing should address any suggested cause of the hypoglycemia, such as ethanol or other drug ingestion. If factitious hypoglycemia is suggested, testing for insulin antibodies or low levels of C peptide may be helpful. A patient who is surreptitiously administering exogenous insulin will have normal to low levels of C peptide and markedly elevated insulin levels.
Management

In alert patients with mild symptoms, oral consumption of sugar-containing foods or beverages is often adequate. In other patients, after blood is drawn for glucose determination, one to three ampules of 50% dextrose in water (D50W) is administered intravenously while the patient’s airway, breathing, and circulation are assessed and maintained. Augmentation of the blood glucose level by administration of an ampule of D50W may range from less than 40 mg/dL to more than 350 mg/dL. These therapeutic steps are appropriately performed in the field if out-of-hospital care is available. If alcohol abuse is suggested, thiamine is administered. D50W should not be used in infants or young children because venous sclerosis can lead to rebound hypoglycemia. In a child younger than 8 years, it is advisable to use 25% (D25W) or even 10% (D10W) dextrose. D25W may be prepared by diluting D50W 1:1 with sterile water. The dose is 0.5 to 1 g/kg body weight or, using D25W, 2 to 4 mL/kg.

If intravenous access cannot be rapidly obtained, 1 to 2 mg of glucagon may be given intramuscularly or subcutaneously. The onset of action is 10 to 20 minutes, and peak response occurs in 30 to 60 minutes. It may be repeated as needed. Glucagon may also be administered intravenously; 1 mg has an effect similar to that of one ampule of D50W. Glucagon is ineffective in causes of hypoglycemia in which glycogen is absent, notably alcohol-induced hypoglycemia.

Families of type 1 diabetic patients are often taught to administer glucagon intramuscularly at home. Of the families so instructed, only 9 to 42% actually inject the glucagon when it is indicated. Intranasal glucagon has not been widely used. Out-of-hospital care providers and emergency physicians should seek a history of glucagon administration because it alters initial blood glucose readings.

All patients with severe hypoglycemic reactions require aspiration and seizure precautions. Although the response to intravenous administration of glucose is generally rapid, older patients may require several days for complete recovery.

Treatment of hypoglycemia secondary to oral hypoglycemic agents depends on the agent. Metformin and the thiazolidinedione agents rarely cause significant or prolonged hypoglycemia, whereas sulfonylureas, which are insulin secretagogues, do cause hypoglycemia. Sulfonylurea oral hypoglycemic agents pose special problems because the hypoglycemia they induce tends to be prolonged and severe. Patients with an overdose of sulfonylurea hypoglycemic agents should have a minimum observation period of 24 hours if hypoglycemia is recurrent in the ED after management of the initial episode. Patients at risk for hypoglycemia from oral sulfonylureas include patients with impaired renal function, pediatric patients, and patients who are naïve to hypoglycemic agents. Although symptoms may occur after an overdose, several case reports in patients with renal failure and pediatric patients describe refractory hypoglycemia after ingestion of a single pill. One case series of pediatric patients presenting with sulfonylurea ingestion who were euglycemic initially demonstrated an average time to onset of 8 hours to the initial hypoglycemic episode.4 However, onset of symptoms was delayed up to 18 hours in some patients. As a result, we recommend 23 hours of observation for patients with known or suspected ingestion of hypoglycemic agents.

A patient with hypoglycemia from sulfonylureas, in addition to standard glucose replacement, frequently requires treatment with an agent to inhibit further insulin release, such as octreotide, a somatostatin analogue. Several case series have described the use of octreotide in both adult and pediatric patients suffering from sulfonylurea-induced hypoglycemia, frequently reporting successful results with a significant decrease in the number of episodes of recurrent hypoglycemia. A randomized clinical trial concluded that patients receiving octreotide had a decreased glucose supplementation requirement.4 No single set protocol for use has been described; however, typical adult doses have ranged from 50 to 100 µg intravenously or subcutaneously every 12 hours, and pediatric dosages have ranged from 25 to 50 µg intravenously or subcutaneously. Whereas experience thus far with octreotide has been positive, it does not obviate the need for prolonged observation and serial glucose measurements.

Disposition

Type 1 diabetic patients with brief episodes of hypoglycemia uncomplicated by other disease may be discharged from the ED if a cause of the hypoglycemia can be identified and corrected by instruction or medication. All patients should be given a meal before discharge to ensure their ability to tolerate oral feedings and to begin to replenish glycogen stores in glycogen-deficient patients. Patients who are discharged should receive short-term follow-up for ongoing evaluation. Patients with hypoglycemia caused by long-acting sulfonylurea medications should be observed in the hospital if they have recurrent hypoglycemia after a period of observation in the ED. Other agents, such as metformin, do not typically produce hypoglycemia, although they may have other issues, such as lactic acidosis, that may require admission.

Nondiabetic Patients

Hypoglycemia in the nondiabetic patient may be classified as postprandial or fasting. The most common cause of postprandial hypoglycemia is alimentary hyperinsulinism, such as that seen in patients who have undergone gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy. Fasting hypoglycemia is caused when there is an imbalance between glucose production and use. The causes of inadequate glucose production include hormone deficiencies, enzyme defects, substrate deficiencies, severe liver disease, and drugs. Causes of overuse of glucose include the presence of an insulinoma, exogenous insulin, sulfonylureas, drugs, endotoxic shock, extrapancreatic tumors, and a variety of enzyme deficiencies.

Emergency treatment is similar to that of hypoglycemia in the diabetic patient. The determination of inpatient versus outpatient evaluation of hypoglycemia in a nondiabetic patient should be based on the suggested cause and the nature of the episode (i.e., factors such as severity, persistence, and recurrence).

DIABETIC KETOACIDOSIS

Principles of Disease

Pathophysiology

DKA is a syndrome in which insulin deficiency and glucagon excess combine to produce a hyperglycemic, dehydrated, acidic patient with profound electrolyte imbalance. All derangements producing DKA are interrelated and are based on insulin deficiency (Fig. 126-1). DKA may be caused by cessation of insulin intake or by physical or emotional stress despite continued insulin therapy.

The effects of insulin deficiency may be mimicked in peripheral tissues by a lack of either insulin receptors or insulin sensitivity at receptor or postreceptor sites. When the hyperglycemia becomes sufficiently marked, the renal threshold is surpassed and glucose is excreted in the urine. The hyperosmolarity produced by hyperglycemia and dehydration is the most important determinant of the patient’s mental status.2

Glucose in the renal tubules draws water, sodium, potassium, magnesium, calcium, phosphorus, and other ions from the
Pathophysiology of Diabetic Ketoacidosis

- Increased lipolysis and TG breakdown
- Decreased glucose uptake
- Increased proteolysis

1. Increased FFA in plasma
2. Increased FFA to liver
3. Increased ketogenesis
4. Ketonuria
5. Decreased alkali reserve
6. Acidosis

Hyperglycemia
- Glycosuria
- Osmotic diuresis
- Loss of electrolytes
- Cellular dehydration
- Volume depletion
- Impaired renal function
- Osmotic diuresis

Table 126-1: Average Fluid and Electrolyte Deficits in Severe Diabetic Ketoacidosis

<table>
<thead>
<tr>
<th>WEIGHT</th>
<th>WATER (mL/kg)</th>
<th>SODIUM (mEq/L)</th>
<th>POTASSIUM (mEq/L)</th>
<th>CHLORIDE (mEq/L)</th>
<th>PHOSPHORUS (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤10 kg</td>
<td>100-120</td>
<td>8-10</td>
<td>5-7</td>
<td>6-8</td>
<td>3</td>
</tr>
<tr>
<td>10-20 kg</td>
<td>80-100</td>
<td>8-10</td>
<td>5-7</td>
<td>6-8</td>
<td>3</td>
</tr>
<tr>
<td>≥20 kg</td>
<td>70-80</td>
<td>8-10</td>
<td>5-7</td>
<td>6-8</td>
<td>3</td>
</tr>
</tbody>
</table>

*Per kilogram of body weight.

Circulation into the urine. This osmotic diuresis, combined with poor intake and vomiting, produces the profound dehydration and electrolyte imbalance associated with DKA (Table 126-1). Exocrine pancreatic dysfunction closely parallels endocrine beta cell dysfunction, producing malabsorption that further limits the body’s intake of fluid and exacerbates electrolyte loss.

In 95% of patients with DKA, the total sodium level is normal or low. Potassium, magnesium, and phosphorus deficits are usually marked. As a result of acidosis and dehydration, however, the initial reported values for these electrolytes may be higher than actual body stores. Hypokalemia may further inhibit insulin release.

The cells, unable to receive fuel substances from the circulation, act as they do in starvation from other causes. They decrease amino acid uptake and accelerate proteolysis such that large amounts of amino acids are released to the liver and converted to two-carbon fragments.

Adipose tissue in the patient with DKA fails to clear the circulation of lipids. Insulin deficiency results in activation of a hormone-sensitive lipase that increases circulating free fatty acid (FFA) levels. Long-chain FFAs, now circulating in abundance as a result of insulin deficiency, are partially oxidized and converted in the liver to acetoacetate and β-hydroxybutyrate. This alteration of liver metabolism to oxidize FFAs to ketones rather than the normal process of re-esterification to triglycerides appears to correlate directly with the altered glucagon/insulin ratio in the portal blood. Despite the increased pathologic glucagon-mediated production of ketones, the body acts as it does in any form of starvation to decrease the peripheral tissue’s use of ketones as fuel. The combination of increased ketone production with decreased ketone use leads to ketoacidosis.

The degree of ketosis has been related to the magnitude of release of the counter-regulatory hormones epinephrine, glucagon, cortisol, and somatostatin. Glucagon is elevated fourfold to fivefold in DKA and is the most influential ketogenic hormone. It is believed to affect ketogenesis by reducing the concentration of malonyl coenzyme A and by inhibiting glycolysis. Epinephrine, norepinephrine, cortisol, growth hormone, dopamine, and thyroxine enhance ketogenesis indirectly by stimulating lipolysis.

Acidosis plays a prominent role in the clinical presentation of DKA. The acidic patient attempts to increase lung ventilation to rid the body of excess acid with Kussmaul’s respiration.
Bicarbonate is used up in the process. Acidosis compounds the effects of ketosis and hyperosmolality to depress mental status directly.

Acidemia is not invariably present, even with significant keto-acidosis. Ketoalkalosis has been reported in diabetic patients vomiting for several days and in some with severe dehydration and hyperventilation. The finding of alkalemia, however, should prompt the consideration of alcoholic ketoacidosis, in which this finding is much more common. Whereas these cases are rare, if there is concern for mixed acid-base disorders, an arterial blood gas sample should be obtained instead of a venous gas sample to further delineate the metabolic abnormalities present.

Etiology

Most often, DKA occurs in patients with type 1 diabetes and is associated with inadequate administration of insulin, infection, or myocardial infarction. DKA can also occur in type 2 diabetics and may be associated with any type of stress, such as sepsis or gastrointestinal bleeding. Approximately 25% of all episodes of DKA occur in patients whose diabetes was previously undiagnosed.

Diagnostic Strategies

History

Clinically, most patients with DKA complain of a recent history of polydipsia, polyuria, polyphagia, visual blurring, weakness, weight loss, nausea, vomiting, and abdominal pain. Approximately half of these patients, especially children, report abdominal pain. In children, this pain is usually idiopathic and probably caused by gastric distention or stretching of the liver capsule; it resolves as the metabolic abnormalities are corrected. In adults, however, abdominal pain more often signifies true abdominal disease.

Physical Examination

Physical examination may or may not demonstrate a depressed sensorium. Typical findings include tachypnea with Kussmaul’s respiration, tachycardia, frank hypotension or orthostatic blood pressure changes, the odor of acetone on the breath, and signs of dehydration. An elevated temperature is rarely caused by DKA itself and suggests the presence of infection.

Laboratory Tests

Initial tests allow preliminary confirmation of the diagnosis and immediate initiation of therapy (Table 126-2). Subsequent tests are made to determine more specifically the degree of dehydration, acidosis, and electrolyte imbalance and to reveal the precipitant of DKA.

On the patient’s arrival to the ED, check the serum and urine glucose concentrations and ketone level, electrolyte values, and blood gas. If determination of the pH is the sole concern, venous blood gas samples may be used as there is good correlation between arterial and venous pH. If there is concern for the adequacy of respiratory compensation or concern for a mixed acid-base disorder (such as concomitant metabolic alkalosis from vomiting that may confuse the clinical picture), an arterial blood gas sample should be obtained. Glucose is usually elevated above 350 mg/dL; however, euglycemic DKA (blood glucose ≤ 300 mg/dL) has been reported in up to 18% of patients. Blood gas measurement usually reveals a low pH, with the aforementioned rare exception of a concomitant alkalemia that may result in a pseudonormalization of the pH. Metabolic acidosis with an anion gap is primarily the result of elevated plasma levels of acetoacetate and β-hydroxybutyrate, although lactate, FFAs, phosphates, volume depletion, and several medications also contribute to this condition. Rarely, a well-hydrated patient with DKA may have a pure hyperchloremic acidosis with no anion gap. Again, although rare, there are case reports of a normal anion gap in a patient with DKA if the vomiting has been sufficient to cause a concomitant metabolic alkalosis. If an immediate potassium level is not available through blood gas analysis, an electrocardiogram may indicate elevated potassium levels. Despite initial potassium levels that are normal to high, a total potassium deficit of several hundred mEq/L results from potassium and hydrogen shifts.

Other laboratory tests in DKA are driven by the clinical picture. A complete blood count may be used to rule out other concomitant issues, such as anemia. The white blood cell count has limitations discussed later. Whereas patients with milder degrees of DKA may not have the severe volume deficits seen in the more severe cases, measurement of blood urea nitrogen and creatinine to evaluate renal function is reasonable. Decisions about volume replacement need to be made irrespective of whether an azotemia is noted on blood chemistry testing. DKA has classically been associated with deficits of magnesium and phosphorus; whereas these deficits are not always clinically significant, it is reasonable to check magnesium and phosphorus levels as occasionally profound deficits of these electrolytes have been noted. Urinalysis, in addition to the presence of ketones, may also help confirm a urinary tract infection as a precipitant of DKA. Use of blood or urine cultures should be determined by the clinical picture.

The serum sodium value is often misleading in DKA. Sodium is often low in the presence of significant dehydration because it is strongly affected by hyperglycemia, hypertriglyceridemia, salt-poor fluid intake, increased gastrointestinal and renal losses, and insensible loss. When hyperglycemia is marked, water flows from the cells into the vessels to decrease the osmolar gradient, thereby creating dilutional hyponatremia. Lipids also dilute the blood, thereby further lowering the value of sodium. Newer autoanalyzers remove triglycerides before assay, thus eliminating this artifact.

Hypertriglyceridemia is common in DKA because of impaired lipoprotein lipase activity and hepatic overproduction of very-low-density lipoproteins. In the absence of marked lipidemia, the true value of sodium may be approximated by adding 1.3 to 1.6 mEq/L to the sodium value on the laboratory report for every 100 mg/dL glucose above the norm. Thus, if the laboratory reports a serum sodium value of 130 mEq/L and a blood glucose value of 700 mEq/L, the total serum sodium value is more accurately assessed to be between 137.8 and 139.6 mEq/L.

Acidosis and the hyperosmolality induced by hyperglycemia shift potassium, magnesium, and phosphorus from the intracellular to the extracellular space. Dehydration produces hemococoncentration, which contributes to normal or high initial serum potassium, magnesium, and phosphorus readings in DKA, even with profound total body deficits. The effect of acidosis on the

<table>
<thead>
<tr>
<th>Table 126-2</th>
<th>Typical Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DKA</strong></td>
<td><strong>HHS</strong></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>&gt;350</td>
</tr>
<tr>
<td>Sodium (mEq)</td>
<td>low 130s</td>
</tr>
<tr>
<td>Potassium (mEq)</td>
<td>~4.5–6.0</td>
</tr>
<tr>
<td>Bicarbonate (mEq)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>25–50</td>
</tr>
<tr>
<td>Serum ketones</td>
<td>Present</td>
</tr>
</tbody>
</table>
serum potassium determination can be corrected by subtracting 0.6 mEq/L from the laboratory potassium value for every 0.1 decrease in pH noted in the arterial blood gas analysis. Thus, if the potassium is reported as 5 mEq/L and the pH is 6.94, the corrected potassium value would be only 2 mEq/L, representing severe hypokalemia. Whereas insulin is administered and the hydrogen ion concentration decreases, the patient needs considerable potassium replacement. Finally, hyperglycemia and the anion gap have significant effects on the plasma potassium concentration, independent of acidosis. No conversion factor has been developed for estimation of true magnesium levels, although initial values may be high.

All laboratory determinations must be interpreted with caution. Serum creatinine determinations made by autoanalyzer may be falsely elevated. Leukocytosis more closely reflects the degree of ketosis than the presence of infection. Only the elevation of band neutrophils has been demonstrated to indicate the presence of infection, with a sensitivity of 100% and a specificity of 80% from a single small retrospective study. Historically, the diagnosis of pancreatitis in a patient with DKA could be confounded by elevation of amylase levels in DKA. Given the strength of the current literature demonstrating greater specificity of lipase for diagnosis of pancreatitis, lipase should be the blood test of choice if pancreatitis is a concern.

**Differential Considerations**

Alcoholics, especially those who have recently abstained from drinking, with Kussmaul’s respiration, a fruity odor to the breath, and acidic arterial blood gas values may have alcoholic ketoacidosis. These patients may be euglycemic or hypoglycemic, and a large part of their acidosis is often caused by the unmeasured β-hydroxybutyric acid. Alcoholic ketoacidosis accounts for approximately 20% of all cases of ketoacidosis.

Ketoacidosis can also develop with fasting in the third trimester of pregnancy and in nursing mothers who do not eat. The differential diagnosis for DKA is broad and includes any entity that may cause elevated anion gap acidosis, ketosis, or both. The presence of DKA should not exclude investigation for other causes of anion gap metabolic acidosis, such as sepsis, poisoning, or lactic acidosis, as physiologic stress from one of these other causes can precipitate DKA.

**Management**

**General Measures**

The approach to the patient with severe DKA is the same as that to any patient in extremis. The comatose patient, especially if vomiting, requires intubation. Once the patient is intubated, maintain hyperventilation to prevent worsening acidosis. The patient in hypovolemic shock requires aggressive fluid resuscitation with 0.9% saline solution rather than pressors; consider other possible causes of shock (e.g., sepsis or myocardial dysfunction secondary to myocardial infarction). Close monitoring of vital signs is essential. Bedside ultrasonography may be of benefit in excluding other causes of hypotension and evaluating the volume status of an individual patient. For example, use of the Focused Assessment with Sonography for Trauma (FAST) examination to exclude pericardial tamponade or hemoperitoneum, if it is clinically indicated, may be helpful. Likewise, evaluation of myocardial contractility and inferior vena cava diameter can help evaluate cardiac function and volume status noninvasively. Although it is not routinely used in the ED setting, in cases in which the volume status is difficult to ascertain because of complex underlying physiologic derangements, such as congestive heart failure and renal failure, invasive hemodynamic monitoring may be required to guide fluid therapy. Routine use of invasive hemodynamic monitoring is not supported by available evidence.

The diagnosis of DKA is generally simple. When hyperglycemia, ketosis, and acidosis have been established, begin fluid, electrolyte, and insulin therapy (Box 126-1).

**Insulin**

DKA cannot be reversed without insulin, and insulin therapy should be initiated as soon as the diagnosis is certain. There are no randomized trials comparing insulin with placebo or other therapies in DKA. However, the mortality from DKA was 90% in historical controls before development of exogenous insulin and 50% after insulin was introduced; with appropriate supportive therapy, it has reached the current levels of 5 to 7%. In the past, very high dosages of insulin were administered to diabetic patients in DKA because they were thought to be extremely insulin resistant. However, several clinical trials done in the 1970s showed that low-dose insulin therapy is as effective as high-dose therapy.

Whereas the dosing of insulin infusions has been established, the utility of an intravenous bolus before the infusion remains controversial and is no longer routinely recommended. More recently, in selected patients with mild DKA, the subcutaneous or intramuscular administration of insulin has been proved safe and as effective as the intravenous administration of insulin. In selected cases with good outpatient follow-up, treatment of DKA with intermittent bolus dosing of regular insulin by the subcutaneous

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**Box 126-1 Summary of Treatment of Diabetic Ketoacidosis**

Identify diabetic ketoacidosis: serum glucose concentration, electrolyte values, ketone level, and arterial blood gas analysis; also obtain complete blood count with differential, urinalysis, chest radiograph, and electrocardiogram, if indicated.

**Supplement insulin.**

- **Insulin replacement:** 0.1 unit/kg/hr regular insulin IV
- **Change IV solution to D₅W0.45% NS when glucose concentration is ≤300 mg/dL.**

**Rehydrate.**

- 1-2 L NS IV during 1-3 hours
- Children: 20 mL/kg NS during first hour
- Follow with 0.45% NS

**Correct electrolyte abnormalities.**

- **Potassium:** Usually unnecessary to replenish
- **Phosphorus:** Usually unnecessary to replenish
- **Magnesium:** Correct with 1-2 g MgSO₄. Serum magnesium levels may not correlate with body stores.

**Correct acidosis.**

- Correction of acidosis is done by administration of IV fluids and insulin.
- Search for and correct underlying precipitant.

**Monitor progress and keep meticulous flow sheets.**

- **Vital signs**
- **Fluid intake and urine output**
- **Serum glucose, K⁺, Cl⁻, HCO₃⁻, CO₂, pH**
- **Amount of insulin administered**
- **Admit to hospital or intensive care unit.**
- **Consider outpatient therapy in children with reliable caretaker and**
  - **Initial pH ≥ 7.35**
  - **Initial HCO₃⁻ ≥ 20 mEq/L**
  - **Can tolerate oral fluids**
  - **Resolution of symptoms after treatment in emergency department**
  - **No underlying precipitant requiring hospitalization**
or intramuscular routes without admission has also been shown to be safe. However, this strategy has not been used in sicker patients. Poor perfusion may hamper the absorption of intramuscular or subcutaneous insulin, resulting in erratic absorption. The current therapy of choice as recommended by the ADA is regular insulin infused at 0.1 unit/kg/hr up to 5 to 10 units/kg/hr, mixed with the intravenous fluids.

Children with DKA pose additional management challenges. Whereas the general principles of fluid and electrolyte repletion in concert with insulin therapy remain the same, controversy exists about the dosing and administration of fluids and insulin because of concerns related to the risk of inducing cerebral edema in children with DKA. Despite frequently voiced concerns about this complication, it remains rare with an overall incidence of 1% in pediatric DKA patients. Virtually all current evidence supporting the contention that the use of higher doses of insulin and aggressive fluid resuscitation contributes to the development of cerebral edema comes from retrospective reviews and small case studies. The best available evidence shows associations only with lower arterial Pco₂ and higher blood urea nitrogen levels, indicating that severity of disease, rather than treatment interventions, plays the most significant role. DKA-related cerebral edema is virtually unheard of in children older than 5 years, and good prospective data are needed to help guide recommendations. Currently, there is an ongoing clinical trial to prospectively assess risk and outcomes (clinicaltrials.gov).

Because the half-life of regular insulin is 3 to 10 minutes, insulin should be administered intravenously by constant infusion rather than by repeated bolus. When the blood glucose concentration has dropped to 250 to 300 mg/dL, add dextrose to the intravenous fluids to prevent iatrogenic hypoglycemia and cerebral edema. In patients with euglycemic DKA, add dextrose to the intravenous fluids at the start of insulin therapy.

Insulin resistance occurs rarely in diabetic patients and requires an increase in dosage for a satisfactory response to be obtained. Resistance may be caused by obesity or accelerated insulin degradation.

**Dehydration**

The severely dehydrated adult patient is likely to have a fluid deficit of 3 to 5 L. No uniformly accepted formula exists for the administration of fluid in this disorder.

If the patient is in hypovolemic shock, administer normal saline (NS) as rapidly as possible in the adult or in boluses of 20 mL/kg in the child until a systolic pressure of 80 mm Hg is obtained. In the adult who has marked dehydration in the absence of clinical shock or heart failure, 1 L of NS may be administered in the first hour. In general, 2 L of NS during the first 1 to 3 hours is followed by a slower infusion of half-NS solution. DKA patients without extreme volume depletion may be successfully treated with a lower volume of intravenous fluid replacement. NS solution at 20 mL/kg during the first hour is the usual fluid resuscitation therapy for a child. Thereafter, adjust the fluid rate according to age, cardiac status, and degree of dehydration to achieve a urine output of 1 to 2 mL/kg/hr. Data do not support use of colloidal over isotonic crystallloid fluids for resuscitation.

Fluid resuscitation alone may help lower hyperglycemia. Because a low level of circulating insulin may be present even in DKA, increased perfusion may transport insulin to previously unreached receptor sites. In addition, a large volume of glucose may be cleared by the kidneys in response to improved renal perfusion. The mean plasma glucose concentration has been noted to drop 18% after administration of saline solution without insulin. Whereas fluid administration decreases serum glucose concentration and improves acidosis, the underlying insulin deficiency in DKA still requires administration of insulin for correction of ketoacidosis. Thus, fluid resuscitation is an important factor in management of DKA but is not sufficient therapy by itself.

Acidosis also decreases after fluid infusion alone. Increased perfusion improves tissue oxygenation, thus diminishing the formation of lactate. Increased renal perfusion promotes renal hydrogen ion loss, and the improved action of insulin in the better-hydrated patient inhibits ketogenesis.

**Potassium**

Potassium replacement is invariably needed in DKA. The initial potassium level is often normal or high despite a large deficit because of severe acidosis. Potassium levels often plummet with correction of acidosis and administration of insulin. Administer potassium with the fluids while the laboratory value is in the upper half of the normal range and monitor renal function. In patients with low serum potassium concentration at presentation, hypokalemia may become life-threatening when insulin therapy is administered; therefore, intravenous administration of potassium in concentrations of 20 to 40 mEq/L is required.

It was once believed that there was always a phosphorus deficit in DKA. As a result, after initial potassium administration was completed with potassium chloride, potassium phosphate was used for follow-up potassium administration to correct the phosphorus deficit. There is no scientific evidence to support this practice, and only isolated case reports support concerns about clinically significant hypophosphatemia in DKA. If the measured serum phosphorus is low, it should be replaced with potassium phosphates.

**Magnesium**

Magnesium deficiency is a common problem in patients with DKA without renal disease. Both the initial pathophysiologic process and the therapy for DKA induce profound magnesium diuresis. Magnesium deficiency may exacerbate vomiting and mental changes, promote hypokalemia and hypocalcemia, or induce fatal cardiac dysrhythmia. The normal person requires 0.30 to 0.35 mEq/kg/day. Thus, it is reasonable to include 0.35 mEq/kg of magnesium in the fluids of the first 3 to 4 hours; further replacement depends on blood levels and the clinical picture. This amounts to 1.0 to 3 g of magnesium sulfate in the 70-kg patient.

**Acidosis**

Bicarbonate therapy may be indicated in severely acidic patients (pH ≤ 7.0). The use of bicarbonate is not warranted in less ill patients for several reasons.

1. Bicarbonate worsens the inhibition of oxygen release from red blood cells caused by the 2,3-diphosphoglycerate deficiency seen in phosphorus-depleted patients with DKA.

2. Overly rapid correction of acidosis is contraindicated because the blood-brain barrier is much more permeable to carbon dioxide than to bicarbonate. Thus, the correction of intravascular acidosis terminates Kussmaul’s respiration, further augmenting the blood carbon dioxide available to cross the blood-brain barrier. Slowly, sufficient bicarbonate crosses the blood-brain barrier to provide adequate buffering. In the short term, however, as the blood acidosis is corrected, the acidity of the fluid surrounding the brain increases, causing paradoxical cerebrospinal fluid acidosis. The clinical significance of an acidic cerebrospinal fluid pH is unclear.

3. The administration of bicarbonate increases the potassium requirement, both immediately by driving potassium into the cell and more gradually by affecting the kidney, making iatrogenic hypokalemia more likely. When bicarbonate is
used, serum potassium levels need to be followed even more closely.

4. The overaggressive use of bicarbonate may produce alkalosis, which induces dysrhythmias largely through its effect on the distribution of electrolytes. Alkalemia occurring late in the course of therapy is more common in patients who have received bicarbonate because ketones are metabolized to carbon dioxide, water, and bicarbonate.

5. Evidence suggests that lowered pH produces a feedback mechanism that directly inhibits ketogenesis. Bicarbonate can increase ketonuria and delay the fall in serum ketones compared with saline infusion alone.

6. Patients treated with bicarbonate fare no better and possibly fare worse than patients treated without bicarbonate. Studies indicate that bicarbonate worsens the prognosis even in patients with severe acidosis and pH values in the range 6.9 to 7.1. It is possible to manage severe DKA with fluids and insulin alone. When this is done, pH normalization is similar to that in a bicarbonate control group.

Given this, there is not a scenario in which bicarbonate administration can be recommended. There is no literature that demonstrates any improvement in outcomes from administration of bicarbonate, even in severely acidemic patients.

Complications

The precipitating causes of DKA may have associated morbidity and mortality rates equal to or worse than those of DKA itself. These include iatrogenic causes as well as infection and myocardial infarction. Morbidity in DKA is largely iatrogenic: hypokalemia from inadequate potassium replacement, hypoglycemia from inadequate glucose monitoring and failure to replenish glucose in intravenous solutions when serum glucose concentration drops below 250 to 300 mg/dL, alkalosis from overaggressive bicarbonate replacement, and pulmonary edema from overaggressive hydration.

The mortality rate in treated DKA is approximately 5 to 7%. The primary causes of death remain infection (especially pneumonia), arterial thromboses, and shock. The decrease in mortality rate demonstrates that appropriate therapy can make a difference. Cerebral edema remains an important cause of morbidity and mortality in children with DKA, but its causes remain unclear.

Consider cerebral edema when the patient in DKA remains comatose or lapses into coma after the reversal of acidosis. It generally occurs 6 to 10 hours after the initiation of therapy. There are no warning signs, and the associated mortality rate is currently 90%. Cerebral edema is rare in adults or children older than 5 years and appears to be most strongly associated with severity of illness (acidemia and azotemia). Subclinical cerebral edema in children is probably common. Furthermore, subclinical cerebral edema may either precede or follow the onset of therapy, raising the question of whether this entity is caused by therapy or is simply a manifestation of the basic pathophysiologic mechanism of DKA. The treatment of cerebral edema is largely supportive and outcomes are poor. No large clinical trials have identified effective treatments for this entity, although some authors recommend mannitol. Steroids have not been shown to be effective.

Disposition

Most patients with DKA require hospital admission, often to the intensive care unit. All pregnant diabetic patients in DKA require admission and consultation with an endocrinologist and obstetrician specializing in the care of high-risk pregnancies. Some children (initial pH ≥ 7.35, bicarbonate ≥ 20 mEq/L) with resolution of findings who can tolerate oral fluids after 3 or 4 hours of treatment may be discharged home with a reliable caregiver. Patients who have mild DKA may be treated on an outpatient basis if the patient or parent is reliable, the underlying causes do not require inpatient therapy, and close follow-up is pursued.

HYPERGLYCEMIC HYPEROSMOLAR STATE

HHS represents a syndrome of acute diabetic decompensation characterized by marked hyperglycemia, hyperosmolarity and dehydration, and decreased mental functioning that may progress to frank coma. The terminology has changed recently from the former hyperglycemic hyperosmolar nonketotic coma, as some patients have mild degrees of ketosis and coma is not universally present. Ketoacidosis is generally minimal or absent, although metabolic acidosis from another source, such as lactic acidosis from sepsis or uremia from acute renal failure, may be present. Focal neurologic signs may be present, or there may be a global encephalopathy. DKA and HHS may occur together.

Principles of Disease

Pathophysiology

As with DKA, the pathophysiologic mechanism of HHS varies with the particular patient. Because most patients with HHS are elders, decreased renal clearance of glucose produced by the decline of renal function with age often contributes to the illness. As with DKA, decreased insulin action results in glycogenolysis, gluconeogenesis, and decreased peripheral uptake of glucose. The hyperglycemia pulls fluid from the intracellular space into the extracellular space, transiently maintaining adequate perfusion. Soon, however, this fluid is lost in a profound osmotic diuresis, limited finally by hypotension and a subsequent drop in the glomerular filtration rate (GFR). The urine is extremely hypotonic, with a urine sodium concentration between 50 and 70 mEq/L, compared with 140 mEq/L in extracellular fluid. This hypertonic diuresis produces profound dehydration, leading to hyperglycemia, hypernatremia, and associated hypertonicity. Often the patient is prevented from taking in adequate fluids by stroke, Alzheimer’s disease, or other diseases, greatly exacerbating the dehydration.

The reason for the absence of ketoacidosis in HHS is unknown. FFA levels are lower than in DKA, thus limiting substrates needed to form ketones. The most likely reason for the blunted counter-regulatory hormone release and lack of ketosis seems to be the continued secretion of tiny amounts of insulin that block ketogenesis.

Etiology

HHS is a syndrome of severe dehydration that results from a sustained hyperglycemic diuresis under circumstances in which the patient is unable to drink sufficient fluids to offset the urinary losses. The full-blown syndrome does not usually occur until volume depletion has progressed to the point of decreased urine output.

HHS is most common in elders with type 2 diabetes but has been reported in children with type 1 diabetes. HHS may occur in patients who are not diabetic, especially after burns, parenteral hyperalimentation, peritoneal dialysis, or hemodialysis.

Clinical Features

The prodrome of HHS is significantly longer than that of DKA. Clinically, extreme dehydration, hyperosmolarity, volume depletion, and CNS findings predominate. If they are awake, patients
may complain of fever, thirst, polyuria, or oliguria. Approximately 20% of patients have no known history of type 2 diabetes. The most common associated diseases are chronic renal insufficiency, gram-negative pneumonia, gastrointestinal bleeding, and gram-negative sepsis. Approximately 85% of patients have underlying renal or cardiac impairment as a predisposing factor. Arterial and venous thromboses are common and often complicate the picture.

The patient often exhibits orthostatic hypotension or frank hypotension, tachycardia, and fever with signs of marked dehydration. The depression of the sensorium correlates directly with the degree and rate of development of hyperosmolarity. Some patients have a normal mental status. Neurologic issues are common in HHS. Whereas decreased level of consciousness is the most common neurologic finding, seizures, stroke syndromes, and movement disorders have been reported in various case series. Whether HHS is the cause of or the result of these disorders is unclear, and there is no evidence currently to recommend use of antiepileptics or antithrombotic agents prophylactically in HHS patients.

Differential Considerations

The differential diagnosis of HHS is identical to that of DKA. In addition, diabetic patients receiving chlorpropamide are subject to water intoxication with dilutional hyponatremia, which may be manifested as coma without acidosis that is clinically indistinguishable from HHS. The patient with HHS who has a sharply depressed sensorium may not be initially distinguishable from the patient with profound hypoglycemia. When blood glucose concentration cannot be rapidly checked, the immediate administration of one ampule of D$_5$W minimally worsens HHS and may be lifesaving for patients with hypoglycemia.

Management

The fluid, electrolyte, and insulin regimens for the initial resuscitation in HHS are subject to the same controversies as the therapies for DKA (see Box 126-1). There are varying recommendations about which intravenous fluids to administer, generally based on calculations of water deficits. There are no well-done randomized trials comparing isotonic versus hypotonic fluid resuscitation, and use of an isotonic crystalloid is a reasonable choice in the volume-depleted patient. Cerebral edema has been noted in isolated case reports in adults, especially with glucose levels above 700 mg/dL. An association between intravenous fluid resuscitation and cerebral edema has not been shown in the literature; previous reports of this association may have been due to the confounder that it is seen in sicker patients who often receive more aggressive fluid resuscitation.

Dehydration

For patients in coma or hypovolemic shock, initial intravenous fluid infusion is given as rapidly as possible. Add glucose to resuscitation fluids when the blood glucose level drops below 300 mg/dL. Because many HHS patients are elders with coexisting diseases, such as congestive heart failure and renal failure, noninvasive or invasive forms of hemodynamic monitoring may be required to guide fluid administration when there is the clinical suspicion of pulmonary edema or volume overload.

Electrolytes

Measurement of serum electrolytes should be used to guide replacement in the HHS patient. In particular, because the degree of acidosis is generally less, potassium levels more accurately reflect total body stores than they do in DKA.

Insulin

The pathophysiologic mechanism of HHS is different from that of DKA, and there is usually enough basal insulin function to prevent frank ketoacidosis. Therefore, a continuous intravenous insulin infusion is not required in these patients as it is with DKA. However, there are times when the use of an intravenous insulin infusion may be of benefit to help lower glucose concentration in a more controlled fashion, particularly in patients with very high glucose levels (>700 mg/dL) or in those who are severely hypoperfused, in whom intramuscular or subcutaneous insulin absorption may be erratic. If an intravenous insulin infusion is used, it should be done at an infusion rate similar to that for DKA (0.1 unit/kg/hr).

Other Considerations

A vigorous search for the underlying precipitant of HHS should be pursued. Response to therapy should be followed in the manner described for patients in DKA. Phenytoin (Dilantin) is contraindicated for the seizures of HHS because it is often ineffective and may impair endogenous insulin release.$^1$ Low-dose subcutaneous heparin may be indicated to lessen the risk of thrombosis, which is increased by the volume depletion, hyperviscosity, hypotension, and inactivity associated with HHS.

Complications

Reasons for high morbidity and mortality rates are not always clear, but many patients with HHS are elders who have underlying cardiac and renal disease. Pediatric HHS differs from adult HHS in that children have a much higher incidence of fatal cerebral edema. Other causes of morbidity and mortality are similar to those described for DKA. The mortality rate of treated HHS patients has been 40 to 70% in the past but now ranges from 8 to 25%.$^{15}$

Disposition

In general, patients with HHS require hospitalization for intravenous hydration, glucose control, and evaluation of precipitating and complicating conditions.

Late complications of diabetes cause significant morbidity and mortality. They develop approximately 15 to 20 years after the onset of overt hyperglycemia. The Diabetes Control and
Complications Trial showed that tight glycemic control significantly reduces the risk of microvascular disease, such as microalbuminuria (the earliest sign of nephropathy), neuropathy, and retinopathy, but at the expense of greatly increasing the risk of recurrent hypoglycemia.¹

**Vascular Complications**

Diabetes is associated with an increased risk for atherosclerosis and thromboembolic complications, which are a major cause of morbidity and premature death. The cause of accelerated atherosclerosis is unknown, although it is probably related to oxidated low-density lipoprotein and increased platelet activity. Atherosclerotic lesions are widespread, causing symptoms in many organ systems. Coronary artery disease and stroke are common. Diabetic patients have an increased incidence of silent myocardial infarction, complicated myocardial infarctions, and congestive heart failure. Peripheral vascular disease is noted clinically by claudication, nonhealing ulcers, gangrene, and impotence. In addition, standard treadmill stress tests have a decreased sensitivity in the detection of coronary artery disease in diabetics. For this reason, exercise or pharmacologic stress echocardiography or a nuclear medicine imaging study should be considered when a provocative test is needed to evaluate the diabetic patient for acute coronary syndrome.¹

**Diabetic Nephropathy**

Renal disease is a leading cause of death and disability in diabetics. Approximately half of end-stage renal disease in the United States is caused by diabetic nephropathy. Diabetic nephropathy involves two pathologic patterns: diffuse and nodular. Clinical renal dysfunction does not correlate well with the histologic abnormalities. Disease usually progresses from enlarged kidneys with elevated GFR, to the appearance of microalbuminuria, to macroproteinuria with hypertension, reduced GFR, and renal failure. The appearance of microalbuminuria correlates with the presence of coronary artery disease and retinopathy.

Azotemia generally does not begin until 10 to 15 years after the diagnosis of diabetes. Progression of renal disease is accelerated by hypertension. Meticulous control of diabetes can reverse microalbuminuria and may slow the progression of nephropathy. Blood pressure should be aggressively managed; angiotensin-converting enzyme inhibitors are effective in controlling hypertension and lowering microalbuminuria. Chronic hemodialysis and renal transplantation are unfortunate endpoints for many diabetic patients with renal disease.

**Retinopathy**

Diabetes is a leading cause of adult blindness in the United States. Approximately 11 to 18% of all diabetic patients have treatable diabetic retinopathy ranging from mild to severe and manifested in many forms. The severity of diabetic retinopathy is clearly related to the quality of glycemic control.

Background (simple) retinopathy is found in most diabetic patients who have prolonged disease. Background retinopathy is characterized by microaneurysms, small-vessel obstruction, cotton-wool spots or soft exudates (microinfarcts), hard exudates, and macular ischemia. The characteristics of proliferative retinopathy are new vessel formation and scarring. Complications of proliferative retinopathy are vitreal hemorrhage and retinal detachment, which may ultimately cause unilateral vision loss. The treatment of diabetic retinopathy is photocoagulation.

Maculopathy is background retinopathy with macular involvement. It results primarily in a deficit of central vision. As with proliferative retinopathy, it is vital that the patient be under the care of an ophthalmologist. Laser therapy in the early stages can dramatically alter the course of this disabling disease.

The diabetic patient may present with complaints ranging from acute blurring of vision to sudden unilateral or even bilateral blindness. Less often, diabetic patients have more gradual vision loss caused by the common senile cataract or the “snowflake” cataract, which may disappear as hyperglycemia is corrected. The associated hyperlipidemia of diabetes may lighten the color of retinal vessels, producing lipidemia retinalis. Anterior ischemic optic neuropathy has been reported.

Diabetic patients with retinopathy should be referred to an ophthalmologist. Even in those with normal vision, ophthalmologic procedures may limit visual loss or prevent crises such as neovascular glaucoma.

**Neuropathy**

Both autonomic and peripheral neuropathies are well-known complications of diabetes. The prevalence of peripheral neuropathy ranges from 15 to 60%. The cause of the neuropathy is not clearly understood, but evidence suggests several factors in its development. Neuropathy may result from the effects of diabetic vascular disease on the vasa nervorum. Myoinositol, the polyol pathway, and nonenzymatic glycosylation of protein may have roles. All these factors are related to an elevated blood glucose level. On pathologic examination, segmental demyelination occurs with loss of both myelinated and unmyelinated axons, particularly those affecting the distal part of the peripheral nerve. Neurologic manifestations of diabetes may regress with improved glycemic control.

Several distinct types of neuropathy have been recognized in diabetes. Peripheral symmetrical neuropathy is a slowly progressive, primary sensory disorder manifested bilaterally with anesthesia, hyperesthesia, or pain. The pain is often severe and worse at night. It affects upper and lower extremities, although lower extremities and the most distal sections of the involved nerves are most often affected. There may be a motor deficiency as well. The pain may be very difficult to control; opioid analgesics have been used, but nonopioid medications such as gabapentin, pregabalin, and amitriptyline are preferred. Pregabalin is the newest of these agents and seems to hold the most promise when it is used at higher doses (up to 600 mg/day). Duloxetine at doses of 60 mg/day is also effective. Both pregabalin and duloxetine achieve significant pain control in at least 50% of patients. Gabapentin at 300 mg three times daily has some efficacy, achieving significant pain relief in about a third of patients; amitriptyline 25 mg daily demonstrates similar results. Aldose reductase inhibitors have not proved to be better than placebo. A reasonable approach for the emergency physician is initiation of duloxetine or pregabalin as these have demonstrated the best efficacy in pain control, with the understanding that it may take several days for peak effect to be reached.²

Mononeuropathy, or mononeuropathy multiplex, affects both motor and sensory nerves, generally one nerve at a time. The onset is rapid, with wasting and tenderness of the involved muscles. Clinically noted is sudden onset of wristdrop, footdrop, or paraly- sis of cranial nerves III, IV, and VI.

Diabetic truncal mononeuropathy occurs rapidly in a radicular distribution. In contrast to other mononeuropathies, it is primarily if not exclusively sensory. If it causes pain, it may mimic that of a myocardial infarction or acute abdominal inflammation. Like diabetic mononeuropathy, it may be most bothersome at night and generally resolves in a few months. Whereas diabetic mononeuropathy is often the first clue of diabetes, truncal mononeuropathy is more often found in known diabetic patients.

Autonomic neuropathy occurs in many forms. Neuropathy of the gastrointestinal tract is manifested by difficulty in swallowing,
delayed gastric emptying, constipation, or nocturnal diarrhea. Impotence and bladder dysfunction or paralysis may occur. Orthostatic hypotension, syncope, and even cardiac arrest have resulted from autonomic neuropathy. Diabetic diarrhea responds to diphenoxylate and atropine, loperamide, or clonidine. Orthostatic hypotension is treated by sleeping with the head of the bed elevated, avoidance of sudden standing or sitting, and use of full-length elastic stockings.

The Diabetic Foot. Approximately 20% of hospitalizations in diabetic patients are related to foot problems. Sensory neuropathy, ischemia, and infection are the principal contributors to diabetic foot disease. Loss of sensation leads to pressure necrosis from poorly fitting footwear and small wounds going unnoticed. The most common cause of injury is pressure on plantar bone prominences. Assess all neuropathic foot ulcers for infection, debride devitalized tissue, and obtain radiographs to evaluate for the presence of foreign bodies, soft tissue gas, or bone abnormalities. Weight bearing must be eliminated by total-contact casting.

Not all ulcers are infected. Infection is suggested by local inflammation or crepitation. Conversely, some uninflamed ulcers are associated with underlying osteomyelitis. Most mild infections are caused by gram-positive cocci, such as *Staphylococcus aureus* or streptococci, and may be treated with oral antibiotics with activity against gram-positive organisms, such as trimethoprim-sulfamethoxazole 800/160 mg twice daily, a first-generation cephalosporin such as cephalexin 500 mg four times daily, or clindamycin 300 mg every 6 hours. A strict non–weight-bearing regimen, meticulous wound care, and daily follow-up care are also vitally important to wound healing. This approach may not be possible when patients are deemed unreliable, do not have good home support, or do not have ready access to follow-up care.

Deeper, limb-threatening infections—as evidenced by full-thickness ulceration, cellulitis more than 2 cm in diameter with or without lymphangitis, bone or joint involvement, or systemic toxicity—are usually polymicrobial in origin and caused by aerobic gram-positive cocci, gram-negative bacilli, and anaerobes. These patients require hospitalization and, after culture, broad-spectrum intravenous empirical antimicrobial therapy (Table 126-3), strict non–weight-bearing status, tight glycemic control, early surgical intervention for debridement, and meticulous wound care. Consider occult osteomyelitis in all cases of neuropathic ulceration. Hyperbaric oxygen has been shown to have some efficacy in treatment of complicated infection, especially with anaerobic organisms. Up to one third of patients eventually undergo amputation.

**Infections**

Diabetic patients are more susceptible to complications of infections because of their inability to limit microbial invasion with effective polymorphonuclear leukocytes and lymphocytes. They have an increased incidence of extremity infections and pyelonephritis compared with the general population. In addition, they are particularly susceptible to certain other infections, such as tuberculosis, mucocutaneous candidiasis, intertrigo, mucormycosis, soft tissue infections, nonclostridial gas gangrene, osteomyelitis, and malignant *Pseudomonas* otitis externa. Treatment of diabetic patients with infection includes rapid culture and antibiotics (see Table 126-3), glycemic control, and generally hospitalization.

**Cutaneous Manifestations**

Dermal hypersensitivity is manifested by pruritic, erythematous indurations that occur at insulin injection sites. The declining prevalence of this condition has paralleled the improved purification of insulin. Insulin lipoatrophy likewise seems to be a result of insulin impurities and is manifested as subcutaneous depressions at injection sites. Although lipoatrophy is now more common than dermal hypersensitivity, its prevalence has also declined sharply because of improved insulin preparations. Insulin lipohypertrophy is manifested by raised areas of subcutaneous fat deposits at insulin injection sites. These lesions generally reflect the failure of the patient to rotate injection sites adequately. They resolve spontaneously during months if insulin injection is avoided in the affected areas and sites are properly rotated.

Insulin pumps are often associated with localized skin problems, usually a reaction to the tape securing the tubing and needles. On occasion, sensitivity to the catheters is seen. Skin infections at the site of injection are the most common complication of insulin pumps. Changing the patient to buffered pure-pork from unbuffered beef-pork insulin is the only intervention that seems to reduce the rate of infection. A few patients have been noted to have hard nodules at the injection site. The cause of these nodules is uncertain.

Diabetic patients who use oral hypoglycemic agents may have rashes associated with these medications. After consumption of ethanol, approximately 38% of type 2 patients taking chlorpropamide exhibit a “flush” consisting of redness of the face and neck and a sense of warmth or burning. Patients may demonstrate urticaria in response to both insulin and oral hypoglycemics.

Diabetic skin conditions include fungal infections, acanthosis nigricans, necrobiosis lipoidica diabeticorum, xanthoma diabeticorum, bullous diabeticorum, and diabetic dermopathy. *Acanthosis nigricans* is characterized by a velvety brown-black thickening of the keratin layer, most often in the flexor surfaces. It is the cutaneous marker for a group of endocrine disorders with insulin resistance. *Necrobiosis lipoidica diabeticorum* begins as erythematous papular or nodular lesions, usually in the pretibial area but in other areas as well. The early lesions may contain telangiectasias. These lesions spread and frequently form a single pigmented area. They are often a reaction to the tape securing the tubing and needles. On occasion, sensitivity to the catheters is seen. Skin infections at the site of injection are the most common complication of insulin pumps. Changing the patient to buffered pure-pork from unbuffered beef-pork insulin is the only intervention that seems to reduce the rate of infection. A few patients have been noted to have hard nodules at the injection site. The cause of these nodules is uncertain.

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**Table 126-3**

<table>
<thead>
<tr>
<th>INFECTIOUS CONDITION</th>
<th>ANTIMICROBIALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic foot infection</td>
<td>Mild: consider trimethoprim-sulfamethoxazole 800/160 mg twice daily or clindamycin 300 mg q6h Moderate to severe: clindamycin 600 mg IV q6h ± piperacillin-tazobactam (Zosyn) 3.75 g IV q6h and vancomycin 15 mg/kg IV q12h</td>
</tr>
<tr>
<td>Malignant otitis externa</td>
<td>Oral: ciprofloxacin 500 mg PO twice daily for 10-14 days IV: ceftazidime 2 g IV q8h ± gentamicin 2 mg/kg IV q8h</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>Amphotericin B 1-1.5 mg/kg/day Posaconazole 400 mg twice daily</td>
</tr>
<tr>
<td>Mucocutaneous candidiasis</td>
<td>Ketoconazole 200 mg PO daily; may need several weeks of therapy</td>
</tr>
<tr>
<td>Nonclostridial gas gangrene (including Fournier’s)</td>
<td>Clindamycin 600 mg q6h + third-generation cephalosporin + vancomycin 15 mg/kg q12h</td>
</tr>
</tbody>
</table>
Xanthoma diabeticorum is evidence of the hyperlipidemia associated with diabetes. It is similar to the xanthoma found in non-diabetic hyperlipidemic patients. Xanthomas have an erythematous base and a yellowish hue.

Bullosis diabeticorum is a rare occurrence. Bullae are usually filled with a clear fluid and are most often found on the extremities, especially the feet. The fluid is occasionally slightly hemorrhagic. The bullae usually heal spontaneously without scarring.

Diabetic dermopathy, or “skin spots,” is the most common finding in diabetes. It arises as discrete, depressed, and brownish lesions generally less than 15 mm in diameter and found in the pretibial area.

Resistant, aggressive impetigo or intertrigo suggests diabetes.

**Insulin Allergy**

Insulin allergy is mediated by immunoglobulin E and is manifested by local itching or pain and delayed brawny edema, urticaria, or anaphylaxis. Systemic reactions are usually seen in patients who have previously discontinued insulin and then resumed therapy. Mild reactions may be treated with antihistamines, whereas anaphylaxis must be treated with epinephrine. Patients with significant reactions must be admitted for desensitization.

**DIABETES IN PREGNANCY**

Before the discovery of insulin in 1922, diabetes in pregnancy was associated with a fetal death rate of 60 to 72% and maternal morbidity of approximately 30%. In 1977, a linear relationship between glycemic control and perinatal mortality was discovered. Strict metabolic control is now a goal in all diabetic pregnancies.\(^5\)

Pregnant patients should be watched extremely closely and aggressively treated for impending or actual DKA. For a variety of reasons, pregnant women have a special predisposition to both glucose intolerance and excess ketone production. Although uncommon, DKA may reduce fetal oxygen delivery and cause perinatal asphyxia. Intellectual deficits in offspring have been associated with maternal ketonuria from any cause.

Pregnancy is associated with progression of retinopathy for unknown reasons. Whether pregnancy worsens diabetic nephropathy or hastens the progression to end-stage renal disease is controversial. Although nephrotic syndrome develops in 71% of pregnancies, blood pressure and proteinuria eventually return to first-trimester values. Diabetic nephropathy is associated with an increased risk of preterm labor, stillbirth, neonatal death, fetal distress, and intrauterine growth retardation; otherwise, the literature is sparse on the effect of pregnancy on diabetic neuropathy. Autonomic neuropathy, particularly gastroparesis, makes adequate nutrition difficult for both mother and fetus. Pregnant women should be referred for parenteral feedings if conservative therapy fails to control vomiting.

Hypoglycemia is common in pregnancy, in part because of intensive insulin treatment to maintain euglycemia. The effects of hypoglycemia on the fetus are unclear. Ketoacidosis is associated with a 50 to 90% fetal mortality rate.\(^5\)

**NEW-ONSET HYPERGLYCEMIA**

Patients often present to the ED with typical diabetic symptoms such as polyuria, polydipsia, and polyphagia. Many have serum glucose concentrations above 200 mg/dL but are not ketotic. Patients with newly diagnosed hyperglycemia with normal electrolyte values may be treated with intravenous hydration alone or with insulin, often reducing the glucose concentration to 150 mg/dL. In reliable patients whose initial glucose concentration is greater than 400 mg/dL, initiation of oral hypoglycemic therapy may be appropriate, with lifestyle modification. Obtain an HbA\(_1c\) value before initiation of therapy to confirm a diagnosis of diabetes and to establish a baseline. Initial therapy with sulfonylureas is appropriate; glyburide (2.5-5 mg once daily) or glipizide (5 mg once daily) is recommended.\(^1,10\) Metformin may be initiated as well at a dose of 500 mg daily; however, it lowers blood glucose on average only about 100 mg/dL, and newly diagnosed diabetics frequently require additional agents to control their glucose concentration. Patients with kidney disease may have complications from use of either sulfonylureas or metformin and will likely need insulin therapy. Follow-up should be stressed and warning signs of hypoglycemia discussed.

**CONTROL OF DIABETES**

The common oral antidiabetic agents are presented in Table 126-4. There are several preparations of insulin available as well. The major recent advances in insulin preparations (in addition to regular insulin and NPH insulin) are ultra-long-acting and ultra-short-acting insulins. These agents are coming into favor because of better basal insulin levels (long acting) and more rapid onset and shorter duration of action (Humalog) to provide more rapid and predictable sliding scale coverage. Other newer agents include the incretin mimetics, such as exenatide, which is used for type 2 diabetes; it is injectable and used in conjunction with oral agents but not with insulin. Amylin analogues, such as pramlintide, are used with insulin but significantly increase the risk of hypoglycemia.

The basic concepts of the diabetic diet remain unchanged, although many studies emphasize foods and medications that alter glucose absorption. Various high-fiber diets have improved glycemic control. The number of supplements or low glycemic index snacks has risen in the past few years. Exercise continues to be a cornerstone of diabetes management, although care must be taken to balance it with appropriate calorie intake and medication use.

Solid organ pancreas transplants have become more common; several centers have performed combined pancreas and kidney transplants in those with end-stage kidney disease due to diabetic nephropathy. Transplantation ameliorates many secondary complications of diabetes, such as nephropathy, neuropathy,
gastroparesis, retinopathy, and microvascular changes. The percentage of grafts functioning after 1 year and the 1-year survival rate of patients are greater than 75% in selected medical centers. Rejection, post-transplantation pancreatitis, and graft thrombosis as well as other vascular and immunosuppression problems continue to plague transplant recipients.

Hypoglycemia may be associated with significant morbidity and mortality. When the diagnosis is suggested and, if possible, confirmed by laboratory evaluation, initiate therapy immediately.

Hypoglycemia caused by sulfonylurea oral hypoglycemic agents may be prolonged. Patients should be observed for an extended period or hospitalized.

The essential treatment of DKA includes restoration of insulin, correction of dehydration, correction of potassium level, correction of acidosis, and treatment of the underlying cause.

Use of sodium bicarbonate to correct acidosis in DKA has not demonstrated any benefit and may be associated with worse outcomes.

Hyperglycemic hyperosmolar state is most commonly seen in elders with multiple comorbid conditions and is distinguished from DKA by lack of ketoacidosis. In addition to fluid resuscitation and correction of hyperglycemia, treatment should address the underlying cause of the state, which includes infection, myocardial infarction, and cerebrovascular accident.

Diabetic peripheral neuropathy is common and has multiple treatment modalities, including gabapentin, pregabalin, and duloxetine.

Diabetic foot ulcers and other diabetic soft tissue infections (such as gas gangrene and Fournier's gangrene) are frequently polymicrobial and require broad-spectrum antibiotic therapy covering gram-positives, gram-negatives, and anaerobes.

Tight glycemic control is considered to be beneficial in reducing the risk of most major complications of diabetes. This is an important point of patient education for diabetics seen in the ED.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.
References