Diabetes Mellitus, Type 1

COURSE OBJECTIVE: The purpose of this course is to prepare healthcare professionals to appropriately care for patients with type 1 diabetes mellitus (T1DM) by identifying its health effects and evidence-based treatment guidelines, as well as the actions necessary to manage the disease.

LEARNING OBJECTIVES:
Upon completion of this course, you will be able to:

- Differentiate type 1 diabetes from type 2 diabetes.
- Describe the epidemiology and pathogenesis of type 1 diabetes.
- Review the current criteria and strategies used to diagnose type 1 diabetes.
- Identify acute and chronic complications of type 1 diabetes and the associated interventions to avoid these complications.
- Discuss self-management of type 1 diabetes.
- Identify strategies to promote adherence to treatment regimens.
- Describe interdisciplinary collaboration as a management strategy.

DIABETES OVERVIEW

Type 1 diabetes mellitus (T1DM) is a serious endocrine condition that must be managed consistently by collaboration between the patient and healthcare providers to prevent serious short- and long-term complications. Careful treatment and patient adherence to lifestyle changes and appropriate therapies are necessary to prevent or minimize these complications.
Commonly referred to as type 1 diabetes, T1DM is a pathologic condition in which the body is unable to properly store and process blood glucose. The monosaccharide (simple sugar) glucose is a critical carbohydrate used by cells as a source of energy. Normally, cells absorb circulating glucose from the blood in response to stimulation by insulin, a hormone produced by the islet cells of the pancreas. In patients with T1DM, a decrease in the concentration of circulating insulin impairs this function. As a result, blood glucose is not properly absorbed by cells and accumulates in the blood, leading to a condition known as hyperglycemia, or high blood glucose levels.

While temporary hyperglycemia with slightly elevated glucose levels is often benign, acute hyperglycemic episodes involving extremely high glucose levels are considered a medical emergency that can result in life-threatening dehydration or coma. Similarly, chronic hyperglycemia may lead to serious complications such as renal failure, neurological damage, blindness, and/or cardiovascular damage.

Although diabetes is a serious disease, patients with T1DM can take several steps to manage their disease and thus lower their risk for complications and premature death.

Impact of Diabetes

In the United States, more than 29 million people have diabetes of any type. Of those, over 8 million people are undiagnosed, suggesting that a large proportion of individuals with diabetes currently go untreated (CDC, 2015).

Although diabetes affects males and females similarly in the United States, racial and ethnic disparities have been identified. National survey data indicate that the prevalence of all types of diabetes in non-Hispanic blacks is nearly twice that of non-Hispanic whites (18.7% versus 10.2%, respectively). Hispanics also seem to be more susceptible to diabetes, with a prevalence of approximately 17%. The prevalence of diabetes among Asian Americans is lowest of all racial and ethnic groups, at 8.4% (CDC, 2015).

The economic impact of diabetes is sizable; in 2012, the total costs related to diabetes in the United States were approximately $245 billion. Although the majority of this amount ($176 billion) was attributed to direct medical costs such as medication and hospitalization, $69 billion was due to indirect costs, including disability, loss of work, and premature mortality. Average medical expenses for patients with diabetes are more than two times higher than those for individuals without diabetes (ADA, 2016a; CDC, 2015).

Even more significant than the economic impact of diabetes are the high morbidity and mortality rates associated with the disease. Diabetes is the seventh leading cause of death in the United States. Deaths in which diabetes is the underlying cause often occur as a result of the many complications associated with the disease. For example, the risk of heart disease and stroke are approximately two to four times higher in patients with diabetes. Other morbidities that occur at a greater frequency among patients with diabetes include hypertension (high blood pressure), blindness, kidney disease, neuropathy (nervous system disease), and limb disease resulting in amputation (CDC, 2015).
Types of Diabetes

Although several types of diabetes are recognized, the vast majority of cases are categorized as either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). **T1DM** (formerly referred to as insulin-dependent diabetes) occurs due to the body’s inability to produce insulin. To overcome this, patients with T1DM self-administer insulin to maintain normal glucose levels. Because it is most often diagnosed among children, adolescents, and young adults, T1DM was also previously known as juvenile diabetes.

Unlike patients with T1DM, patients with **T2DM** produce insulin, but their cells do not properly respond to the hormone. This is the most common type of diabetes, accounting for 90% to 95% of all adult diabetes cases in the United States. T2DM begins as a condition referred to as insulin resistance, in which the body’s cells do not properly use insulin.

T2DM is currently rare among children aged <10 years, but rates among children are increasing overall. Rates of T2DM are greater among youth aged 10–19 years than among younger children, and incidence among U.S. minority populations is higher than among non-Hispanic whites. Overall, the rates of new cases of T2DM among youth in the United States are highest among non-Hispanic blacks and Native Americans/Alaskan Natives (CDC, 2015).

Occasionally, patients cannot be clearly classified as having either T1DM or T2DM. For example, patients who otherwise appear to have T2DM may present with ketoacidosis, which occurs rarely among patients with T2DM. Similarly, patients with T1DM may present with an unusually slow onset of symptoms late in life. Such atypical presentations of diabetes may occur among patients at any age. The true diagnosis in these patients may become apparent only with time.

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<td><strong>Preferred Name</strong></td>
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<tr>
<td>Type 1 diabetes mellitus</td>
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<td>Type 2 diabetes mellitus</td>
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Source: CDC, 2016.

<table>
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<tr>
<th>COMPARISON OF T1DM AND T2DM</th>
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<tr>
<td><strong>Characteristic</strong></td>
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<td>Time of onset</td>
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<tr>
<td>Body type</td>
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<td>Insulin requirement</td>
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Pathophysiology

| Insulin deficiency; pancreas is usually damaged by an autoimmune attack | Insulin resistance; pancreas produces insulin, but the cells do not properly respond to the hormone |

Source: CDC, 2016.

**Gestational diabetes**, another form of the disease, arises from glucose intolerance during pregnancy. Generally affecting women who are obese or who have a family history of diabetes, it requires treatment in order to avoid complications in the infant. Women who develop gestational diabetes have a 35% to 60% chance of developing T2DM in the 10 to 20 years following pregnancy (CDC, 2011).

In addition to T1DM, T2DM, and gestational diabetes, the American Diabetes Association (ADA) recognizes an intermediate group of individuals whose glucose levels, although not meeting formal criteria for diabetes, are too high to be considered normal. These persons are referred to as having impaired fasting glucose (fasting plasma glucose [FPG] levels of 100 to 125 mg/dL) or impaired glucose tolerance (two-hour values in the oral glucose tolerance test [OGTT] of 140 to 199 mg/dL). Individuals with impaired fasting glucose and/or impaired glucose tolerance have been referred to as having **prediabetes**, indicating a high risk for the future development of diabetes (ADA, 2016e).

**EPIDEMIOLOGY**

Interestingly, the incidence of T1DM varies worldwide. The rate of T1DM in the United Kingdom is similar to that of the United States. However, among European countries, the highest rates of T1DM occur in the northern part of the continent, while the lowest rates are in the southern region. Even the lower rates of T1DM present in southern Europe are still greater than those in Asian countries such as China and Japan, which share the lowest worldwide prevalence.

In the United States, T1DM accounts for 5% to 10% of all cases of diabetes in adults. In addition, nearly 20,000 people younger than 20 years of age are diagnosed with T1DM each year in the United States. Unlike T2DM, T1DM is more common among non-Hispanic whites than non-Hispanic blacks or Hispanics. Asian Americans and Native Americans have the lowest incidence of T1DM of all racial and ethnic groups in the United States (CDC, 2015).

T1DM occurs most frequently in children and adolescents. In fact, it is the most commonly occurring pediatric metabolic disease. The annual incidence of T1DM in patients younger than 19 years of age is approximately 19 cases per 100,000 individuals. Overall, approximately 1 in every 400 children and adolescents in the United States currently has T1DM (ADA, 2016b; CDC, 2015).

T1DM typically presents in children ≥4 years of age, with a peak incidence of onset between 11 and 13 years of age. Despite its propensity to occur in younger persons, T1DM also affects adults, where it most commonly appears in individuals in their late 30s to early 40s.
T1DM in adults is typically caused by a loss of pancreatic function, resulting in reduced or no insulin production. For example, loss of pancreatic function may occur as a consequence of chronic pancreatitis, in which repeated and prolonged inflammatory episodes cause damage or death of the insulin-producing cells of the pancreas (Levitisky & Madhusmita, 2016).

**Risk Factors**

Unlike with T2DM, few risk factors have been identified for T1DM. Additionally, no risk factor has been shown to be solely responsible for the development of T1DM, suggesting that the disease arises as the result of a number of triggers.

A patient’s risk for eventually developing T1DM can be quantified by measuring levels of specific **biomarkers** (molecules indicating an autoimmune reaction against the pancreatic islet cells). For example, the presence of antibodies against the pancreatic islet cells, or directed against insulin itself, are both suggestive of an autoimmune reaction that can cause T1DM.

**FAMILY HISTORY**

One risk factor for the development of T1DM is family history. Individuals with a first-degree relative (i.e., parent, child, or sibling) diagnosed with T1DM are at a significantly greater risk for developing the disease themselves (Atkinson, 2012).

**GENETIC FACTORS**

Genetic factors are also linked to the development of T1DM. The majority of genes associated with T1DM are categorized as human leukocyte antigen (HLA) genes; together, **HLA genes** contribute up to 50% of the genetic risk for T1DM. Certain HLA genotypes confer an increased risk for the development of T1DM, while other HLA genotypes are associated with a decreased risk for the disease.

Genetic factors promoting development of T1DM must be more common among non-Hispanic whites because people of that ethnic group experience the highest rate of T1DM. As the understanding of genetic factors that lead to T1DM increases, genetic tests may help to identify patients likely to develop the disease (ADA, 2016b; ADA, 2016c).

The genetic component of T1DM is especially notable among identical twins, among whom there is a concordance rate of approximately 40%. The fact that this rate is not significantly higher among identical twins suggests, however, that environmental factors have a role in the pathogenesis of T1DM (Pietropaolo, 2014).

**ENVIRONMENTAL FACTORS**

**Dietary components** during infancy are one example of environmental factors that may affect development of T1DM and T2DM. Among these dietary factors, short duration of breastfeeding and early introduction of solid food and cow’s milk to infants are leading candidates. Short
breastfeeding duration was suggested as a possible risk factor in the wake of evidence showing that breastfeeding for less than one year and/or a lack of breastfeeding increases the risk for development of T1DM and T2DM later in life (Patelarou et al., 2012). The evidence for early introduction of solid food and cow’s milk as risk factors is more controversial, and some studies show no evidence to support this.

Viral infection is another possible environmental risk factor for T1DM. The connection between viral infection and the onset of T1DM is unclear, but it may be that viral exposure triggers an autoimmune response targeting the insulin-producing cells of the pancreas. Alternatively, the virus itself may target these cells, damaging them and rendering them incapable of effectively producing insulin. Viruses suggested to play a role in the pathogenesis of T1DM include the Epstein-Barr virus, coxsackievirus, the mumps virus, and cytomegalovirus (Coppieters et al., 2012).

DIABETES SECONDARY TO OTHER CONDITIONS

Medical conditions that damage or destroy pancreatic cells, such as chronic pancreatitis or pancreatic surgery, can cause diabetes. Some genetic disorders (Klinefelter syndrome, Huntington’s chorea, Wolfram syndrome, leprechaunism, Rabson-Mendenhall syndrome, lipodystrophic diabetes, and others) and hormonal conditions (acromegaly, Cushing syndrome, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma) also increase patients’ risk for developing diabetes (Dholakia et al., 2016; Matsumoto et al., 2016; Rekittke et al., 2016).

DEVELOPMENT OF TYPE 1 DIABETES

The amount of sugar in the blood is increased after a person eats. This rise in blood glucose normally triggers the release of insulin from the pancreas. The major function of insulin is to stimulate the removal and storage of glucose from the blood into body cells to allow the glucose to be used later by the body for energy. As a result of this process, blood glucose levels return to normal.

In patients with diabetes, blood glucose levels are not properly reduced by these mechanisms because of the body’s inability to produce insulin. As a result, without insulin therapy, blood glucose levels remain elevated (Khardori, 2015).

Normal Physiology of Glucose Regulation

Glucose is a sugar that the body uses as an essential fuel. The extent to which blood glucose levels rise is dependent on the amount and type of food eaten as well as other factors, including the rate of digestion. After eating, glucose crosses the gut wall and enters the body’s bloodstream. Because of its chemical structure, glucose absorption across the gut wall is dependent on specialized glucose transporters. The levels of blood glucose are not constant; rather, they fluctuate throughout the day depending on consumption of food and the body’s
energy needs. In addition to food, another primary source of glucose for the body is the breakdown of glycogen in the liver and muscles.

Although the regulation of glucose levels in the blood is maintained by a number of pathways, including removal by the liver, chief among these is the insulin pathway. Insulin is produced in and released from the pancreatic islet cells. After a meal, glucose enters the pancreatic islet cell through a glucose transporter. When the cell detects the rise in glucose, it responds by secreting insulin into the bloodstream. Once it is released, insulin has a very short half-life due to its rapid degradation by enzymes.

On a cellular level, insulin acts by binding to insulin receptors located on the surface of the body’s cells. By doing this, insulin stimulates muscle and fat cells to remove glucose from the bloodstream. Other functions of insulin include triggering cells to metabolize glucose to produce energy (in the form of ATP) and stimulating cells to utilize glucose during protein synthesis. Insulin also triggers the body to store glucose as glycogen for a short-term energy reserve and as fat for a long-term energy reserve.

**Pathology of Type 1 Diabetes**

T1DM is caused by destruction of the insulin-producing pancreatic islet cells. Because this destruction is typically caused by the body’s immune system, T1DM (unlike T2DM) is considered an autoimmune disorder. The exact cause of this autoimmune reaction is unclear but is likely due to one or more of several factors, including genetics, environmental triggers, pathogens (i.e., viruses), and infant dietary factors (see above).

Over time, as more and more pancreatic islet cells become damaged, the body’s insulin levels begin to drop. Eventually, the body can no longer produce enough insulin to properly manage blood glucose regulation, resulting in hyperglycemia. In some cases, however, patients experience what is referred to as a “honeymoon period” shortly after T1DM is diagnosed, during which the patient’s diabetic symptoms diminish or disappear for a period of a few months to a year. Insulin needs can become minimal during this time, and some patients may indeed find they can maintain normal or near-normal blood glucose levels with little or no insulin administration.

It would be a mistake, however, to assume that the diabetes has gone away during this period. Because T1DM occurs when approximately 90% of the body’s pancreatic islet cells have been destroyed, most patients are still producing a small amount of insulin when T1DM is diagnosed. Over time, however, the process that destroyed 90% of the insulin-producing cells in the patient’s pancreas will ultimately destroy the remaining cells. As that destructive process continues, the amount of insulin the patient requires will increase, and ultimately the patient will be totally dependent on insulin injections to normalize blood glucose levels.
DIAGNOSIS

Diabetes is clinically diagnosed based on chronic hyperglycemia. However, hyperglycemia and/or some of the other symptoms associated with diabetes can also arise from a number of unrelated medical conditions. Therefore, alternative explanations should be explored. For example, some medications have been found to cause hyperglycemia, and discontinuation of these drugs results in a normalization of blood glucose levels.

MEDICATIONS THAT CAN CAUSE HYPERGLYCEMIA

The following medications can cause hyperglycemia, and they may cause or worsen hyperglycemia in patients with T1DM.

- Systemic corticosteroids (e.g., prednisone)
- Thiazide diuretics (e.g., hydrochlorothiazide)
- Statins (e.g., atorvastatin, simvastatin)
- Atypical antipsychotics (e.g., clozapine, olanzapine)
- Estrogens
- Alpha-interferon

Clinical Examination

Individuals with T1DM may present with any of a variety of symptoms. Unlike the stereotypical presentation of an overweight or obese patient with T2DM, however, patients with T1DM may previously appear healthy and have a normal weight, then present with a sudden onset of several symptoms at once. Rarely, a diagnosis of T1DM may occur as a result of a routine health screening and blood work. More typically, observation of hyperglycemia during a medical examination performed in response to an onset of symptoms over days or weeks alerts the clinician to the possibility of T1DM.

A suspected diagnosis of T1DM prompts a thorough physical examination of the patient. This examination should include a complete medical history, especially addressing the presence of risk factors such as family history of T1DM. Current symptoms are also evaluated. Because symptoms can be subtle, the patient may need to be asked specifically about the presence of those typical of T1DM. For example, the patient should be asked if they have experienced an increased need to urinate, increased thirst, or increased hunger.

Once a diagnosis of T1DM is confirmed, the patient is followed closely, both to monitor response to treatment as well as to recognize and mitigate complications arising from diabetes. Routine clinical assessment and care, as well as annual physical examinations, provide an opportunity to note the development of these complications. Further, patients diagnosed with T1DM are surveyed for the presence of comorbidities that may worsen in the presence of diabetes (such as hypertension), with referral to a medical specialist as appropriate.
RECOMMENDED ANNUAL EXAMS FOR PATIENTS WITH T1DM

- Annual dilated eye examination by an optometrist or ophthalmologist
- Comprehensive oral examination by a dentist
- Consultation with a mental health professional, if needed, to screen for psychological issues such as anxiety and depression that may develop related to T1DM
- Podiatric evaluation for foot problems, care of toenails, and instructions on foot care

Signs and Symptoms

The hallmark clinical sign of T1DM is hyperglycemia, which is defined as blood glucose levels >130 mg/dL in the fasting state or >180 mg/dL after meals (WebMD, 2015). However, hyperglycemia is a sign of both T1DM and T2DM and therefore cannot be used to aid in the differentiation of these conditions.

The most common symptoms noted by persons with T1DM are polyuria, polydipsia, and polyphagia (Khardori, 2015; Larkin et al., 2014).

- **Polyuria** (the excretion of large volumes of urine) is due to a condition known as osmotic diuresis, or the build-up of substances in the kidney tubules. This increase changes the osmotic pressure within the tubules, thereby inducing water retention. The excess volume is then excreted as urine. In patients with T1DM, hyperglycemia causes glucose to accumulate in the kidney tubules, and thus osmotic diuresis occurs secondary to hyperglycemia. In young children especially, nighttime enuresis (bed-wetting) may be present.

- **Polydipsia** (excessive thirst) often accompanies polyuria. The ingestion of large volumes of liquid contributes to the polyuria experienced by these patients.

- **Polyphagia** (excessive hunger) is another common symptom of T1DM. Despite the consumption of large amounts of food, patients may experience weight loss. In the patient with T1DM, weight loss in the presence of normal food consumption or polyphagia is a result of both dehydration and the catabolic state (due to insulin depletion and the reduced availability of glycogen, proteins, and triglycerides).

- **Fatigue and weakness** is common among patients with T1DM due to catabolic muscle wasting.

- **Muscle cramps** can result from an imbalance in electrolytes, including sodium, chloride, and potassium.

- **Gastrointestinal symptoms** (e.g., nausea, abdominal pain) and **neurologic changes** (e.g., cerebral edema and coma) can be caused by diabetic ketoacidosis (DKA), a dangerous condition that occurs when insufficient insulin levels cause the body to break down fats instead of glucose for energy. DKA may occur if the patient does not adhere to
their prescribed insulin therapy or if the insulin regimen is not properly tailored to the patient’s needs. Alternatively, DKA can be triggered by stress, injury, or illness that alters the balance of insulin and glucose.

- **Peripheral neuropathy** (nerve damage occurring in the extremities) is a frequent symptom of T1DM. This is due to the build-up of sorbitol, a product of glucose conversion in the sensory nerves of the periphery. Patients experience the onset of peripheral neuropathy first as a numbness and tingling sensation in the hands and feet. The extremities are typically affected in a “glove and stocking” pattern. Notably, peripheral neuropathy associated with diabetes is bilateral and symmetrical (this condition is described in more detail later in this course).

- **Blurred vision** can result from glucose-induced swelling of the lens of the eye.

**Diagnostic Tests**

Blood glucose tests are used for the definitive diagnosis of diabetes mellitus. Four blood glucose tests are used for this purpose. While these tests may be used to diagnose diabetes mellitus, they cannot by themselves differentiate T1DM from T2DM (ADA, 2016e).

**FASTING PLASMA GLUCOSE (FPG) TEST**

The FPG test is a measure of the blood glucose level in an individual after a period of fasting. This method assesses the ability of the body to properly store glucose following a meal. It is performed after the patient has not eaten for at least 8 hours and is most reliable when done in the morning.

In the FPG test, normal levels of blood glucose are considered to be <100 mg/dL, while levels between 100 and 125 mg/dL are considered to indicate prediabetes. Blood glucose levels of ≥126 mg/dL indicate diabetes but must be confirmed by repeating the FPG test on a different day.

The FPG test is convenient and low-cost and is therefore a preferred blood glucose test for the diagnosis of diabetes. However, it may not detect some cases of diabetes that would be recognized using other blood glucose tests.

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<tr>
<th>Plasma Glucose Level (mg/dL)</th>
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<td>&lt;100</td>
<td>Normal</td>
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<tr>
<td>100–125</td>
<td>Prediabetes</td>
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<tr>
<td>≥126</td>
<td>Diabetes*</td>
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* Confirmed by repeating the test on a different day.

Sources: ADA, 2016d; ADA, 2016e.
ORAL GLUCOSE TOLERANCE TEST (OGTT)

The OGTT measures blood glucose levels in an individual who has fasted for at least 8 hours and is administered 2 hours after that person has consumed a glucose-containing liquid. This method assesses the ability of the body to tolerate an influx of glucose. Generally, the liquid is composed of 75 grams of glucose dissolved in water.

Using the OGTT test, blood glucose levels of <140 mg/dL are considered normal, between 140 and 199 mg/dL indicate prediabetes, and ≥200 mg/dL are diagnostic of diabetes. As with the FPG test, a positive diagnosis of diabetes using the OGTT must be repeated on a different day for confirmation.

Although less convenient than the FPG test, the OGTT test has been shown to be more sensitive and therefore more reliable in detecting diabetes.

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* Confirmed by repeating the test on a different day.

Source: ADA, 2016e.

GLYCOXYLATED HEMOGLOBIN (A1C) TEST

Under conditions of hyperglycemia, excess glucose enters the red blood cells circulating throughout the blood. Red blood cells also contain hemoglobin, the protein responsible for oxygen transport within the blood. When glucose enters a red blood cell, it links to the hemoglobin molecules, forming glycosylated hemoglobin (HbA1C, commonly referred to as A1C). As glucose levels increase, the amount of glycosylated hemoglobin also increases.

The A1C test is a measure of the percentage of hemoglobin molecules that have glucose molecules attached to them. The A1C value is indicative of the average blood glucose level in an individual over the previous two to three months. Therefore, it is considered a long-term assessment of glucose control. A1C levels less than 6% are considered normal. The ADA (American Diabetes Association) recommends that patients with T1DM should have a goal of achieving A1C levels of less than 7% to reduce the risk for diabetes-related complications.

The A1C test is useful both for monitoring the long-term control of blood glucose levels in a patient with T1DM and in diagnosing the disease. For decades, diagnosis of diabetes was based solely on plasma glucose levels, using either the FPG test or the 2-hour, 75-gram OGTT value.
In 2009, however, a collaborative committee that included representatives of the ADA, the International Diabetes Federation, and the European Association for the Study of Diabetes recommended the use of the A1C test to diagnose diabetes, with a threshold of ≥6.5%, and the ADA adopted this criterion in 2010.

The A1C test has several advantages over the FPG and OGTT due to its greater convenience (i.e., fasting is not required) and the fact that it is less influenced by day-to-day vacillations in blood glucose levels during periods of stress or illness. These advantages must be balanced by the greater cost of A1C testing and the unreliable correlations between A1C and average glucose values in some patients. A1C also inaccurately reflects glycemia in patients with certain anemias and hemoglobinopathies (e.g., sickle cell anemia). However, the previously established glucose criteria for the diagnosis of diabetes (FPG and the OGTT) remain valid as well.

Except in cases when the diagnosis of T1DM is clear based on clinical findings (e.g., when a patient with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL), a test result diagnostic of diabetes should be repeated to rule out laboratory error. It is always preferable that the same test be repeated for confirmation. If results of two different tests (e.g., the A1C and FPG) are both above the diagnostic thresholds for diabetes, however, the diagnosis of diabetes is confirmed.

**RANDOM PLASMA GLUCOSE TEST**

A random plasma glucose test is an informal measure of the blood glucose level. This method is performed at random, with no fasting requirement. Using this test, a blood glucose level of ≥200 mg/dL in the presence of other symptoms may indicate that a patient has diabetes. In the case of a positive random plasma glucose test, a diagnosis of diabetes is confirmed using either an FPG, OGTT, or A1C test.

**TESTING TO DIFFERENTIATE TYPE 1 DIABETES FROM TYPE 2 DIABETES**

Once diabetes mellitus has been diagnosed, it is necessary to establish whether the patient has T1DM or T2DM in order to determine the proper course of treatment (McCulloch, 2016).

- **Insulin levels** can be measured to determine if an individual is producing the hormone. Similarly, levels of C-peptide (a molecule formed when proinsulin is converted to insulin) are also measured to determine whether the patient’s body is producing insulin. An insulin level of <5 µU/mL or a C-peptide test ≤0.6 mg/mL is suggestive of T1DM. Notably, patients with T2DM and a very high blood glucose level may be mistakenly diagnosed as having T1DM due to the decrease in insulin production resulting from the elevated blood glucose levels. Unlike patients with T1DM, these patients will resume normal insulin production once glucose levels are regulated.

- Because T1DM is considered an autoimmune disease, further blood work can be used to test for the presence of autoantibodies. Pancreatic islet cell antibodies are present in nearly 85% of patients with T1DM. Although they may differ, the majority of islet cell
antibodies are directed against glutamic acid decarboxylase (GAD), an enzyme expressed in pancreatic beta cells. Many of these patients also have anti-insulin antibodies.

- A urinalysis may be performed to assay for the presence of ketones, the acidic byproduct of the breakdown of fat molecules. Accumulation of ketones can result in diabetic ketoacidosis (DKA). This condition rarely occurs in patients with T2DM, and therefore their presence in urine is considered indicative of T1DM.

**CASE**

A 35-year-old woman is evaluated by her primary care physician because of an approximate 10-pound weight loss over the previous two months and frequent episodes of increased thirst and increased urination including nocturia. She states she has not been experiencing nausea, vomiting, or abdominal pain, though she admits to increased headaches. The patient has been previously healthy and states she does not consume alcohol, tobacco, or illicit drugs. Her medications include only vitamin supplements, and she is physically sedentary. Her father has had T2DM for 22 years and her sister was diagnosed with T1DM at age 18 years.

Physical examination reveals a white female of normal body weight who is in no acute distress. Mucous membranes are dry, however the rest of the examination findings are normal. Laboratory analysis reveals a blood glucose level of 350 mg/dL, an A1C level of 8.0%, and ketones present in the patient’s urine. She is diagnosed with diabetes and hospitalized overnight for subcutaneous insulin therapy and rehydration by oral fluid therapy.

Over the next 18 hours, the patient’s blood glucose level decreases to 140 mg/dL. She is diagnosed with presumed T2DM and released from the hospital after initial diabetes education regarding diet and exercise. She is also prescribed metformin (Glucophage) and instructed to monitor her blood glucose levels four times daily and advised to see her primary care physician four days after discharge.

The patient returns to her physician’s office three days later complaining of awakening in the middle of the night “feeling shaky.” She also notes continued hyperglycemia, with fingerstick readings typically >300mg/dL. She is then referred to an endocrinologist and, after further testing, found to have T1DM rather than T2DM. The endocrinologist stops the metformin and collaborates with a diabetes educator to educate the patient about insulin therapy and appropriate meal planning. The patient is started on long-acting, once-daily insulin with ongoing blood sugar monitoring both before and after meals. After three months on insulin, the patient’s A1C level is 6.1%, and she has regained four pounds.

**Question:** What clinical testing might the endocrinologist have performed to determine whether the patient had T1DM or T2DM?

**Answer:** Making a correct diagnosis of T1DM versus T2DM can be challenging, in part because the autoimmune destruction of the pancreatic islets cells that produce insulin can occur at any age. Also, although DKA is a common feature of T1DM, it may not be present early in the disease, occurring in only approximately 20% of patients with new-onset T1DM. Antibody
testing is an essential tool in differentiating the diagnosis, as antibodies to pancreatic islet cells or insulin are present in a majority of patients with T1DM. Finally, levels of insulin and C-peptide can be measured to determine whether the patient’s body is producing insulin. Low levels of insulin or C-peptide help confirm the diagnosis.

MANAGEMENT OF TYPE 1 DIABETES

There is presently no cure for T1DM. Instead, it is a chronic and lifelong condition that requires patients to adhere to a prescribed diet and therapeutic regimen. With faithful adherence, patients with T1DM may live a long life and experience less-frequent and less-severe diabetes-related complications. The lifelong commitment these patients must make includes:

- Frequent monitoring of blood glucose levels
- Taking regular doses of insulin
- Following a diet designed to manage blood sugar levels
- Participating in an active exercise routine

The most effective management of T1DM occurs when a multidisciplinary team approach is taken. The multidisciplinary team typically includes primary care providers, nurses, endocrinologists, registered dietitians, and diabetes educators.

One of the major impacts of T1DM is the potential for the development of both acute and chronic complications of the disease. Development of diabetes-related complications may necessitate additional specialists, such as cardiologists, ophthalmologists, dermatologists, podiatrists, physical therapists, occupational therapists, and others. A pediatrician is a crucial member of the care team in the case of juvenile patients with T1DM.

Patients with T1DM must also commit to regular clinician visits to be sure that their disease is properly controlled. The two primary goals of therapy for T1DM are to prevent the development of diabetes-related complications and to keep blood glucose levels near normal.

Preventing and Treating Acute Complications

Acute complications are emergency conditions that can become life-threatening if not immediately treated. The two main acute complications that affect patients with T1DM are hypoglycemia and DKA.

HYPOGLYCEMIA

Hypoglycemia (low blood glucose levels) is a serious side effect that can occur in patients with T1DM. Normally, decreased blood glucose levels trigger the pancreatic hormone glucagon to activate the breakdown of glycogen within cells, causing the release of glucose into the bloodstream. This results in restoration of normal blood glucose levels. However, this response is
impaired in patients with T1DM, whose disease is controlled by insulin therapy. Because of their lifelong dependence on insulin treatment, patients with T1DM have an increased likelihood of experiencing hypoglycemia compared to patients with T2DM.

**Recognizing Hypoglycemia**

Hypoglycemia may occur when patients with T1DM take a dose of insulin but then miss a meal, have a strenuous exercise workout, or for some reason deplete their blood glucose. It is sometimes referred to as an **insulin reaction**. Consumption of alcoholic beverages may also cause hypoglycemia in T1DM diabetics. In addition to insulin therapy itself, the injectable medication pramlintide, which is administered in conjunction with insulin to patients with T1DM, is associated with a risk of hypoglycemia.

Short or mild cases of hypoglycemia can cause weakness and fatigue. Prolonged or serious cases are more dangerous, causing confusion, clumsiness, or unconsciousness. Especially severe cases may lead to irreversible brain damage, seizures, comas, and ultimately death.

Hypoglycemia can have a very sudden onset, and early symptoms may appear to be mild. Patients with T1DM should be made aware of the danger associated with hypoglycemia and educated to recognize its symptoms so that they can intervene before the condition becomes serious.

**SYMPTOMS OF HYPOGLYCEMIA**

- Weakness
- Fatigue
- Hunger
- Shakiness
- Nervousness
- Sweating
- Dizziness
- Light-headedness
- Sleepiness
- Confusion
- Difficulty speaking
- Anxiety

Because a normal night’s sleep can mean that patients experience a prolonged period without a meal, T1DM patients should also be informed that hypoglycemia can occur during sleep. It is important to occasionally monitor blood glucose levels during the night to determine whether they become too low.
SIGNS OF HYPOGLYCEMIA DURING SLEEP

- Crying out or experiencing nightmares
- Damp pajamas or sheets due to excessive perspiration
- Feeling tired, irritable, or confused after waking up

Treating and Preventing Hypoglycemia

When patients recognize the onset of hypoglycemic symptoms, they should immediately check their blood glucose levels. Levels below 70 mg/dL require immediate intervention. A variety of “quick-fix” sugar-filled foods provide a simple and quick means to raise blood glucose levels (Myers, 2011).

QUICK-FIX FOODS TO TREAT HYPOGLYCEMIA*

- Glucose tablets (3 to 4 tablets)
- Glucose gel (1 serving, equivalent to 15 grams of carbohydrate)
- Fruit juice (4 ounces)
- Regular (not diet) soft drink (4 ounces)
- Milk (8 ounces)
- Hard candy (5 to 6 pieces)
- Sugar or honey (1 tablespoon)

* Listed amounts are for adults and may be decreased for children.

Once patients consume one of these quick-fix foods, they should recheck their blood glucose level 15 minutes later to be sure it has increased to 70 mg/dL or above. If not, they should consume another serving of one of these sugar-containing foods. Either way, this quick-fix intervention should be followed by a snack after the blood glucose level has returned to normal if the next scheduled snack or meal is more than 1 to 2 hours away (ADA, 2016b).

Because of their propensity to develop hypoglycemia, patients with T1DM should be instructed to always have one of these quick-fix interventions available to them.

Because cases of moderate to severe hypoglycemia can cause patients to lose consciousness or otherwise be unable to help themselves, they should wear a medical identification bracelet or a medical alert tag. A family member, coworker, or care provider can be trained to give an injection of glucagon, which causes blood glucose levels to be rapidly restored to normal.
Frequent episodes of hypoglycemia may be a sign that the patient’s blood glucose levels are not being effectively managed. These patients could benefit from a different meal plan, a new insulin administration schedule, or a modified physical exercise routine.

Patients with T1DM should be educated regarding strategies to prevent and treat hypoglycemia. Frequent monitoring of blood glucose levels can help patients identify activities that cause them to develop hypoglycemia; this is particularly important when they undertake new physical activities. Patients should be instructed to always have several servings of high-glucose “quick-fix” foods available to treat hypoglycemia if it occurs. Other strategies include encouraging patients with T1DM to carry a medical alert wallet card and to discuss with friends, family, and coworkers how to handle a hypoglycemic emergency if one occurs.

**DIABETIC KETOACIDOSIS**

DKA is a serious acute complication that may lead to cerebral edema, diabetic coma, and if not treated, death. Although DKA may occur in anyone with diabetes, it is far more common in patients with T1DM compared to those with T2DM (Kitabchi et al., 2014).

This condition occurs when insufficient insulin levels cause the body to break down fats instead of glucose for energy. DKA may occur if the patient does not adhere to his or her prescribed insulin therapy or if the insulin regimen is not sufficient for the patient’s needs. Alternatively, the condition may be triggered by stress, injury, or illness that alters the balance of insulin and glucose.

**COMMON CAUSES OF DKA**

- Infection
- Illness (e.g., pneumonia or influenza)
- Missed insulin dose(s)
- Inadequate insulin dosage
- Stress
- Alcohol abuse
- Surgery
- Trauma

**Diagnosing and Testing for DKA**

The primary evidence that DKA is occurring is the presence of ketones in the urine. Acidic ketones, a byproduct of fat metabolism, become toxic when they accumulate in the blood. Their toxicity is due to their ability to cause acidosis (a drop in blood pH). Normally, the pH of blood is tightly regulated between 7.38 and 7.44; the build-up of ketones in the blood causes the pH to drop to below 7.3. The severity of DKA can be
established with standard laboratory studies and is primarily determined by the blood pH level and bicarbonate level in combination with observing the patient’s mental status.

The onset of DKA may occur in less than 24 hours. Once symptoms of DKA occur, DKA quickly develops into a life-threatening condition in only a few hours. Very early signs of DKA result from hyperglycemia and therefore include thirst, dry mouth, frequent urination, and high blood glucose levels. These signs are followed by other symptoms, often beginning in the gastrointestinal system, such as nausea, vomiting, and abdominal pain. Another symptom of DKA is Kussmaul breathing (also referred to as air hunger), resulting from difficulty breathing. Patients also feel constantly tired, have dry or flushed skin, and appear confused. A fruity odor may be apparent to their breath.

**SYMPTOMS OF DKA**

- Thirst
- Dry mouth
- Frequent urination
- High blood glucose levels
- Nausea and vomiting
- Abdominal pain
- Kussmaul breathing
- Fatigue
- Dry or flushed skin
- Confusion
- Fruity breath odor

Elevated levels of blood ketones is an important sign that a patient’s blood glucose levels are not properly regulated. The presence of ketones can be tested using a simple urine test strip for ketonuria. Because symptoms of DKA may be slow to develop, it is recommended that patients with T1DM test for the presence of ketonuria if their blood glucose levels exceed 250 mg/dL. Additionally, because DKA is more likely to occur when diabetic patients have an illness, a urine test to check for ketonuria should be performed every 4 to 6 hours.

Patients should be educated to contact their healthcare provider for guidance if a urine test reveals an accumulation of ketones. Patients should also be warned not to exercise if they experience elevated ketone levels, as this can cause blood glucose levels to rise further.
Treating and Preventing DKA

Most patients require hospitalization for treatment of DKA. While patients with mild DKA may be treated at home under observation, the guidelines for patients to be admitted to the hospital for therapy include blood glucose levels over 250 mg/dL, an arterial blood pH level below 7.3, a serum bicarbonate level of less than 15 mEq/L, and moderate to high levels of ketones present in their urine.

The treatment priorities for a patient with DKA include protection and maintenance of the airway and treatment for shock, if present. If the underlying cause of DKA is an infection or illness, the patient should be treated for those as well.

Currently, the standard of care for patients with DKA includes an intravenous insulin drip. Additionally, the patient is administered fluids and electrolytes, especially to restore potassium balance.

All patients diagnosed with DKA should receive education to prevent reoccurrence of the condition. The importance of compliance with their insulin regimen should be stressed, especially if poor compliance precipitated the DKA episode. In addition, patients should carefully monitor their blood glucose levels and test their urine for the presence of ketones if their blood glucose levels exceed 250 mg/dL.

CASE

A 3-year-old girl presents for care to her pediatrician after one week of bedwetting at night. Her mother explains that the child has also been hungrier and thirstier than usual for the past two weeks and urinates frequently during the day. She has complained of abdominal pain for the past two days but has had no diarrhea or vomiting. The mother states that her child had a viral illness with high fever approximately two months prior. The illness resolved, but she has noticed the girl being increasingly irritable.

Upon physical examination and comparison to her past growth records, the pediatrician notes that the child has lost two pounds over the past six months. Her skin has poor turgor, and mucous membranes appear dry. She additionally has signs of thrush, with a white coating on her tongue. Urinalysis reveals the presence of glucose and ketones in her urine, and blood glucose evaluation by glucometer reveals a result of 810 mg/dL, leading the pediatrician to suspect T1DM with DKA. The patient is therefore admitted to the hospital for treatment and observation. Her candidal infections resolved with her improved blood sugar control.

Question: What is appropriate treatment for a patient newly diagnosed with T1DM and DKA?

Answer: DKA is a medical emergency, as patients with DKA are at risk for cerebral edema, coma, and death. The treatment of a patient with new onset T1DM with DKA requires admission to the hospital for intravenous fluid rehydration, insulin drip therapy to control blood glucose levels, and close monitoring of vital signs, neurological status, blood gases, blood glucose levels, and electrolytes. DKA can cause shifts in potassium levels that can result in
arrhythmias, difficulty breathing, and fatigue. These patients are hospitalized for several days to allow medical stabilization and, once stabilized, initiation of diabetic teaching by a multidisciplinary care team, often coordinated by an endocrinologist.

Diabetic teaching of the patient and family includes providing information about meal planning, blood glucose measurement, insulin therapy, managing illnesses and infections, managing hypoglycemia, and controlling hyperglycemia to prevent long-term complications. The family should also receive psychosocial support (e.g., referral to a family therapist), as needed, regarding stress they may be experiencing regarding the patient’s illness. Ongoing medical supervision of patient care is typically performed by an endocrinologist in collaboration with primary care providers.

CASE

An 11-year-old boy is brought by his mother to see his nurse practitioner because of a one-week history of excessive urination, excessive thirst, hunger, and complaints of fatigue. His mother reports that she received a call from a friend’s mother stating that the boy had been up seven to eight times at night to urinate during a sleepover at their home. He has experienced no abdominal pain, nausea, vomiting, or visual changes during this period of time. He has lost one pound in weight since his last clinic visit six months ago. The patient has been previously healthy and has no family history of T1DM.

The patient presents as a happy, active boy. Results of his laboratory studies reveal a random blood glucose reading by glucometer of 260 mg/dL, with the presence of glucose but no ketones in the boy’s urine. His renal function tests are within normal limits. Based on these findings and an accompanying A1C level of 8.6%, the nurse practitioner diagnoses the patient with presumed T1DM without DKA.

Question: What is appropriate treatment for a patient newly diagnosed with T1DM without DKA?

Answer: In the absence of DKA, the focus of therapy is on stabilization of blood glucose levels, beginning insulin therapy, diet planning for the patient, and teaching the patient and family to manage diet and insulin therapy to prevent periods of hypoglycemia and hyperglycemia.

For example, in this patient’s case, the nurse practitioner would prescribe insulin therapy and arrange for his family to be instructed in how to use a glucometer at home to measure the child’s blood glucose levels four times a day. His blood glucose levels may be stabilized by treatment with a long-acting insulin, but daily glucose monitoring is necessary to ensure that he does not need additional short acting insulin at mealtimes. The family would then be provided with dietary planning information and instructed to return to the office for follow-up evaluation (e.g., in four days) to evaluate the effect of the insulin therapy and the family’s comfort with blood sugar measurement and to reinforce teaching about insulin administration and diet.
The nurse practitioner could also refer the patient and his family to a multidisciplinary diabetes care team (e.g., at a local hospital) for further information about meal planning, insulin therapy, blood glucose measurement, managing illnesses and infections, managing hypoglycemia, and controlling hyperglycemia to prevent long-term complications. The family should also receive psychosocial support regarding stress they may be experiencing regarding the patient’s illness. Ongoing medical supervision of patient care is typically performed by an endocrinologist in collaboration with primary care providers.

(See also “Patient and Family Teaching and Follow-Up” later in this course.)

Preventing and Treating Chronic Complications

Chronic complications may also become serious or life-threatening but typically develop only over an extended period of time after the patient has been living with T1DM for one or more decades. Chronic complications typically result from damage caused by continual or frequent hyperglycemia.

One of the most important interventions to prevent the frequency and severity of chronic complications related to T1DM is to maintain blood glucose levels as close to normal as possible. This long-term therapeutic goal is a commitment for the patient.

Because theirs is a chronic disease, patients have a lifelong increased risk for these complications. If a patient does develop a disease complication, early recognition and intervention are critical to prevent a worsening of disease.

CARDIOVASCULAR CONDITIONS

Patients with T1DM have an increased risk for a number of cardiovascular complications, including heart disease, stroke, and hypertension (NIDDK, 2013).

Because of the seriousness of cardiovascular complications, patients with T1DM should be counseled to follow their diabetic diet, get regular aerobic exercise, and undergo regular screening for risk factors, signs, and symptoms of cardiac disease. A cardiac stress test is indicated for patients in whom cardiovascular complications are suspected. In addition, patients should be educated to watch for warning signs of cardiovascular disease and stroke.

Atherosclerosis

The primary cause of cardiovascular complications in diabetics is increased atherosclerosis. Atherosclerotic plaques have a propensity to form in diabetic patients as a result of three major mechanisms: 1) the glycosylation (addition of a sugar molecule) of proteins and lipids within the arterial wall; 2) oxidative stress; and 3) activation of the enzyme protein kinase C, which leads to the expression of growth factors that induce the thickening of the arterial wall (Schnell et al., 2013).
Atherosclerosis occurs as a result of the build-up of fatty material deposits on the arterial wall. As these deposits accumulate, the vessel narrows, reducing and eventually impairing blood flow. (Source: NHLBI, 2015.)

**WARNING SIGNS OF A MYOCARDIAL INFARCTION**

- Chest pain
- Pain in the shoulder, jaw, neck, or arms
- Lightheadedness
- Diaphoresis
- Anxiety
- Pallor

**Stroke**

If the patient experiences warning signs of a stroke, he or she should contact emergency personnel immediately. If a stroke is suspected, several tests will be performed. The patient should be examined for changes in body function such as the ability to move his or her arms and legs, to read, or to describe an image. Computed tomography (CT) scans or magnetic resonance imaging (MRI) may be used to image the brain, looking for signs of blood vessel damage. Additionally, a cerebral arteriogram may be used to determine if
the arteries leading to the brain are narrowed or blocked; in this exam, a dye is injected into a catheter that is positioned in an artery in the neck.

Immediate intervention is critical to reduce the damage caused by a stroke. “Clot-busting” drugs are used to help dissolve clots blocking blood flow from the heart to the brain. However, these drugs are only useful if given promptly (within three hours) after the first symptoms of a stroke appear. Therefore, it is important that T1DM diabetic patients—as well as their families, coworkers, and friends—be taught to recognize the warning signs of a stroke.

**WARNING SIGNS OF A STROKE**

- Weakness or numbness on one side of the body
- Sudden onset of confusion or difficulty in understanding
- Difficulty speaking
- Dizziness and loss of balance
- Difficulty walking
- Inability to see out of one or both eyes, or double vision
- Severe headache

**Hypertension**

Hypertension (high blood pressure) is another serious cardiovascular complication that may develop in patients with T1DM. Because hypertension can add to the already present risk of stroke, cardiac disease, and other complications in diabetic patients, the ADA and the National Institutes of Health recommend a lower blood pressure target (120/80 mmHg) in individuals with diabetes compared with the general public.

Hypertension can occur without warning, and many patients do not realize their blood pressure is elevated. Therefore, patients with T1DM should have their blood pressure monitored at every office visit. If hypertension is discovered, lifestyle interventions should be recommended to help lower the blood pressure. These can include an improved diet, weight loss, exercise, and limiting alcohol consumption and tobacco use.

In addition to lifestyle changes, antihypertensive medications may be prescribed. The type and amount of the medication will depend on the specific needs of each individual patient.
ANTIHYPERTENSIVE MEDICATIONS

<table>
<thead>
<tr>
<th>Class</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme (ACE) inhibitors</td>
<td>Prevent the formation of angiotensin, leading to blood vessel relaxation</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers (ARBs)</td>
<td>Prevent the activity of angiotensin, resulting in blood vessel relaxation</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Cause the heart to beat more slowly and less forcefully</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Decrease the force of contraction of the heart</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Help to eliminate extra body fluids</td>
</tr>
</tbody>
</table>

DIABETIC NEUROPATHY AND FOOT COMPLICATIONS

Diabetic neuropathy is one of the most frequent complications experienced by patients with T1DM. Patients may experience a condition known as peripheral neuropathy (also referred to as distal symmetrical polyneuropathy), which frequently begins as a tingling sensation or the feeling of numbness in the toes. These sensations gradually travel upward through the feet, ankles, and lower legs.

As the condition progresses, other extremities begin to be affected, such as the fingers and hands. Notably, these sensations are distributed symmetrically and therefore affect both feet and both hands, resulting in a “glove and stocking” sensation. As the condition worsens and the nerve endings in these extremities become progressively more damaged, the patient begins to lose feeling and experiences a loss of muscle control in these areas (Chiles et al., 2013; NIDDK, 2014e; Pop-Busui, 2014).

SYMPTOMS OF PERIPHERAL NEUROPATHY

- Numbness
- Insensitivity to pain or temperature
- Extreme sensitivity to light touch
- Tingling, burning, or prickling sensation
- Sharp pains or cramps
- Loss of balance and/or coordination

Because peripheral neuropathy is a common complication for diabetic patients, it should be screened for at each clinician visit. Tuning fork, pin-prick testing, and Semmes-Weinstein monofilament testing are commonly used to test the patient’s sensory ability in the upper and lower extremities.
NEUROPATHIES OCCURRING IN PATIENTS WITH T1DM

<table>
<thead>
<tr>
<th>Type</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
<td>Causes pain or numbness in the extremities, including the toes, feet, legs, hands, and arms</td>
</tr>
<tr>
<td>(most common)</td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td>Causes changes in digestion, function of the bowel and bladder, sexual response, perspiration; may also be responsible for a condition known as hypoglycemia unawareness, in which a patient no longer experiences warning symptoms of low blood glucose levels</td>
</tr>
<tr>
<td>Proximal</td>
<td>Causes pain in the thighs, hips, or buttocks</td>
</tr>
<tr>
<td>Focal</td>
<td>Causes a sudden weakness of a nerve or group of nerves (any nerve in the body), causing weakness or pain</td>
</tr>
</tbody>
</table>

Peripheral neuropathy associated with diabetes has no known cure. Treatment for the condition focuses on slowing progression of the disease, relieving pain, managing complications, and reducing neuromuscular symptoms. Consistently keeping blood sugar levels within the patient’s target range can delay the progression of peripheral neuropathy and even cause an improvement in existing symptoms in some patients.

**Treating Associated Pain**

Several medications are used to relieve nerve pain associated with diabetic peripheral neuropathy. These include the anticonvulsant agents gabapentin (Neurontin), pregabalin (Lyrica), and carbamazepine (Tegretol). The side effects of this class of drugs include drowsiness, dizziness, and swelling (Mayo Clinic, 2015a).

The tricyclic antidepressant medications amitriptyline (Tryptomer, Elavil, Tryptizol, Laroxyl, Saroten, Sarotenx, Lentizol, Endep), desipramine (Norpramin, Pertofrane), and imipramine (Tofranil) can provide relief for mild to moderate symptoms for some patients but are associated with a relatively high rate of side effects, including dry mouth, sweating, weight gain, and dizziness.

For some people, the serotonin- and norepinephrine-reuptake inhibitor classes of antidepressant (SNRI) medications (e.g., Cymbalta, Effexor) can relieve pain with fewer side effects. Possible side effects of SNRIs include sleepiness, dizziness, nausea, decreased appetite, and constipation (Mayo Clinic, 2015a).

Lidocaine patches are used effectively in some patients. These patches, which are applied topically to painful skin areas, may cause skin irritation and allergic reaction in some people. Opioid pain relievers, such as tramadol or oxycodone, may be necessary to treat pain successfully in some patients. This class of medications can produce serious side effects, including addiction, constipation, and drowsiness, which make their long-term use undesirable (Mayo Clinic, 2015a).
Complementary and alternative therapies (e.g., the use of capsaicin cream or acupuncture) may be helpful in relieving pain in some patients with diabetic neuropathy. These treatments are usually used in conjunction with medications but may sometimes be effective on their own (Mayo Clinic, 2015a). Transcutaneous nerve stimulation has also been used successfully in the treatment of diabetic neuropathic pain.

**CASE**

A 47-year-old woman with a 21-year history of T1DM is treated by her primary care physician for increasing chronic pain in her feet related to peripheral diabetic neuropathy, which was first diagnosed five years ago. In addition, she has been treated for several foot ulcers over the last six months. Her diabetes is also complicated by diabetic retinopathy, which was successfully treated with laser therapy four years ago. Her past medical history is notable for rheumatoid arthritis. She also has well-managed hyperlipidemia and mild hypertension but shows no signs or symptoms suggestive of renal disease.

For the past three years, the patient’s diabetes has been well controlled by her use of an insulin infusion pump with additional injections of subcutaneous insulin as needed to control postprandial glucose levels. Pain in her feet and hands related to peripheral neuropathy is currently treated with the tricyclic antidepressant imipramine (Tofranil), and she also receives azathioprine (Imuran) and nonsteroidal anti-inflammatory agents for treatment of her arthritis.

**Question:** In light of the patient’s increasing pain related to peripheral diabetic neuropathy, how might her primary care provider alter her treatment plan to provide more effective pain relief?

**Answer:** Interventions for peripheral diabetic neuropathy can be successfully combined for treatment of worsening peripheral pain symptoms, and patients can be counseled in lifestyle changes to slow progression of the nerve damage.

In this case the primary care provider might change the patient’s medication, substituting an anticonvulsant medication (e.g., gabapentin, pregabalin, or carbamazepine) for the tricyclic agent imipramine and recommend the use of an alternative medicine intervention such as capsaicin cream or acupuncture to provide supplemental pain relief. In addition, he or she could recommend the use of lidocaine patches to provide topical analgesia in painful areas of the patient’s feet. More severe cases of peripheral neuropathic pain might require treatment with opioid pain relievers and/or the addition of transcutaneous nerve stimulation to provide additional pain relief.

Patients with peripheral neuropathy should also receive ongoing instruction and encouragement to maintain lifestyle habits that can delay the progression of the damage to the peripheral nerves. These habits include performing careful daily foot care, exercising, avoiding the use of tobacco, and avoiding alcohol or drinking only in moderation. The patient may benefit from a podiatric referral for care to prevent further foot problems.
Addressing Foot Complications

Foot complications arising from peripheral neuropathy are common among patients with T1DM. Nerve damage can cause numbness and a loss of feeling in the feet, and therefore patients with these symptoms are more prone to be unaware of foot discomfort (such as a pebble in the shoe causing a blister) until the damage is already done. Nerve damage also reduces the oil and moisture that is normally supplied to the skin of the foot, causing it to peel, crack, and become very dry (NIDDK, 2014d).

There are also other causes of foot complications in patients with T1DM. Poor blood circulation in the feet occurs due to hyperglycemia-induced narrowing and hardening of the blood vessels. Patients with poor blood circulation in their feet may constantly feel that their feet are cold; however, they should use caution when attempting to warm their feet, as neuropathy-induced loss of feeling may reduce their ability to realize whether their foot is being burned by water or a heating pad that is too warm (NIDDK, 2014d).

Poor blood circulation may also cause a build-up of pressure within the foot, causing calluses that can break down and turn into open sores. These foot ulcers, which occur most often on high-pressure areas such as the ball of the foot or the underside of the big toe, are a common cause of foot infections in diabetic patients. If the ulcer becomes infected, the problem may be compounded by poor blood circulation in the foot (NIDDK, 2014d).

Together, foot complications may ultimately cause the patient to be forced to undergo amputation. In order to prevent amputation, patients should be counseled to maintain appropriate foot care, which may include special therapeutic shoes, cleaning of foot ulcers, professional removal of calluses, and appropriate exercise. Patients should also be encouraged to stop smoking, as smoking contributes to poor blood circulation and the progression of foot complications (NIDDK, 2014d).

AMPUTATION AND PHYSICAL THERAPY

The physical therapist’s initial evaluation after a patient’s amputation includes examination and assessment of the following:

- Skin evaluation (e.g., for scarring, sensation, moisture, lesions)
- Residual limb length (for bone and soft tissue length)
- Residual limb shape (e.g., cylindrical, conical, bulbous end, etc.)
- Vascularity and condition of soft tissue of the residual limb (pulses, color, temperature, edema, atrophic changes)
- Neurological condition of remaining limb tissue (e.g., pain, neuropathy)
- Neurologic status of the patient (cognitive state, emotional status)
Based on the exam and assessment, the physical therapist determines **initial postoperative physical therapy goals** for the patient as follows:

- Promote optimal wound healing
- Monitor the residual limb for shape, incision healing/closure, length, sensory integrity, volume, tissue integrity, color, temperature, and pain
- Edema control
- Scar tissue mobilization around the incision to promote optimal scar shape
- Early preparation of the limb for prosthetic fitting
- Maintenance and optimization of range of motion of the residual limb
- Improvement of the patient’s physical endurance
- Patient education
- In-bed mobility
- Training regarding safe bed-to-chair/wheelchair transfers
- Balance training
- Casting for a training prosthesis approximately 10 to 14 days after the amputation

Patients requiring amputation have traditionally received soft compressive dressings postoperatively to allow complete stump healing prior to initial prosthesis fitting. Patients are now, however, increasingly being treated by immediate postoperative prosthesis placement (IPOP), which allows early initiation of gait training with the practice prosthetic, thereby avoiding prolonged immobility, which can place patients at risk for deconditioning and/or falls with potential for injury to the limb stump.

**Later postoperative physical therapy goals** for the patient will likely include the following:

- Evaluation of the prosthesis for correct fit
- Training in the correct use and care of a customized prosthetic limb
- Gait training, including types of gait deviations (hiking, vaulting,
circumduction, etc.)

- Phantom pain management (interventions include careful inspection of the limb to rule out neuroma or wound infection, use of compression, desensitization techniques, and heat; medications, steroid injections, nerve blocks, and/or relaxation/hypnosis to relieve pain may be prescribed or administered by other licensed healthcare professionals)

- Ongoing skin care of the operative and opposite limb

- Monitoring of the residual limb for reddening and/or skin breakdown from use of prosthesis

- Strengthening exercises of the upper and lower extremities and trunk

Patients who have undergone amputation are typically cared for collaboratively by an interdisciplinary rehabilitation team including physicians, nurses, physical therapist, prosthettist, and occupational therapist. The team may also include a social worker, vocational rehabilitation specialist, and a dietitian, as needed. Collaboration with nursing specifically includes timing pain management interventions to reduce patient discomfort during physical therapy sessions, wound management, training regarding bed and chair/wheelchair transfers, and patient and family education.


**CASE**

A 42-year-old man with a 32-year history of TIDM is admitted for transtibial amputation of his left foot due to a history of severe lower-limb peripheral vascular disease and chronic, infected, nonhealing foot ulcers. After the amputation surgery, he is referred to physical therapy for rehabilitative evaluation and treatment.

**Question:** What constitutes appropriate and inappropriate physical therapy goals for this patient during the immediate, acute-stage post-operative period?

**Answer:** This patient’s care team will focus on a number of goals following the amputation procedure. These will include such things as placement of soft compression dressings or IPOP to the residual limb, training regarding safe bed-to-chair/wheelchair transfers, maintenance and optimization of range of motion of his residual limb, and improvement of his physical endurance. Gait training with an appropriate assistive device might also be initiated. Gait training with the patient’s customized prosthetic limb is not a part of the immediate, acute-stage post-operative physical therapy plan of care. This generally occurs later in the sub-acute or outpatient phase of rehabilitation.

Likely future challenges for this patient may include pain management; decreased strength, range of motion, and/or mobility; decreased skin integrity; decreased endurance; inability or decreased ability to walk, play, and work; and psychological concerns such as depression and anxiety.
KIDNEY DISEASE (NEPHROPATHY)

Patients with T1DM have a high risk for the development of kidney disease (nephropathy). Kidney disease occurs due to high blood glucose levels, causing the organs to filter too high a volume of blood. This increased volume causes the kidneys to become overworked, leading to their inability to keep protein from being filtered out of the blood. As a consequence, protein that would otherwise be useful to the body is filtered into the urine and excreted. The presence of a small amount of protein in the urine is called microalbuminuria. When kidney disease has progressed to later stages and higher levels of protein are present in the urine, this condition is known as macroalbuminuria (ADA, 2016b).

Early intervention is a key step to limiting kidney damage. Tight control of blood glucose levels can help to reduce the risk of microalbuminuria by approximately one third. Several treatments are also available to slow kidney disease when it is caught in the microalbuminuria stage.

Once microalbuminuria develops, tight control of blood glucose levels can significantly reduce the risk of progressing to macroalbuminuria (NIDDK, 2014c). However, once the disease reaches the macroalbuminuria stage, it has progressed to advanced stages and is usually followed by the development of end-stage renal disease (ESRD), which leads to kidney failure.

Because the kidney overworks to compensate for its decreased efficiency, early stages of kidney disease are often not accompanied by symptoms. Therefore, careful monitoring for signs of kidney deficiency at routine check-ups is an important component of care for patients with T1DM. In addition to a urine test to monitor the presence of protein, a blood test can be performed to check for the presence of waste products. It is not until the disease has progressed that the first symptoms may become noticeable. While these may vary from patient to patient, they often begin with fluid build-up. Other symptoms of kidney disease are listed below.
SYMPTOMS OF NEPHROPATHY

- Loss of sleep
- Poor appetite
- Nausea
- Weakness
- Difficulty concentrating

Slight elevations in blood pressure can have a dramatic effect on kidney disease progression; therefore, patients should be counseled to keep their blood pressure levels low. This is preferably done by changes in lifestyle, such as losing weight, decreasing salt intake, avoiding alcohol and tobacco use, and increasing exercise. However, if these methods do not lower the blood pressure levels enough, medications may be used.

Another method to control the progression of kidney disease is to limit the amount of protein in the diet. Because protein contributes to the work the kidney must do, reducing dietary protein can decrease the workload of the organ. However, a patient should only begin a low-protein diet under the care of a physician and with the guidance of a nutritionist.

During ESRD, kidney function is so limited that the patient requires kidney dialysis in order to achieve adequate removal of toxins from the blood. Patients with ESRD who do not have heart or blood vessel disease may qualify for kidney transplantation. Despite the significant risks associated with this procedure, patient survival is dramatically improved with transplantation compared with dialysis. At 86%, the 5-year survival rate for patients receiving a kidney transplant is more than twice the 36% 5-year survival rate for patients treated with dialysis (NIDDK, 2012).

EYE COMPLICATIONS

High blood glucose levels in patients with T1DM also lead to an increased risk of eye complications. Although some of these complications may lead to blindness, many are only minor eye problems. Diabetic retinopathy, the general term used to refer to disorders of the retina that are caused by diabetes, is categorized as two major types (NIDDK, 2015):

- Nonproliferative retinopathy is the most common form of diabetic retinopathy, eventually occurring in nearly all patients with T1DM. In this disorder, the capillaries behind the eye become increasingly blocked, ballooning and forming pouches.

- Proliferative retinopathy, which occurs after several years of retinopathy progression, is a condition in which the capillaries behind the eye become so blocked that new blood vessels are prompted to form in the retina. These new vessels are much weaker and more apt to leak blood, which can distort or block vision. They may also prompt the development of scar tissue, and as this tissue shrinks, it can cause retinal detachment as the retina becomes distorted or pulled out of place.
Retinal damage results primarily from swelling and weakening of the blood vessels. (Source: NIDDK, 2015.)

Early diagnosis of diabetic retinopathy is the key factor in the ability of treatments to limit the resulting vision loss. Because of this, patients with T1DM should be counseled to have a yearly eye exam in which the eye is dilated and examined for evidence of retinopathy.

Photocoagulation is a type of treatment in which a laser is used to produce tiny burns on the retina. These burns seal leaky capillaries, reducing the build-up of blood behind the eye. Although photocoagulation is quite effective when implemented when vision is still normal, it does not work when the retina has already become detached or when a lot of bleeding has occurred. In these cases, the remaining treatment option is a vitrectomy, a surgical resection of the scar tissue and cloudy fluid inside the eye. A vitrectomy is most effective when done prior to retinal detachment.

Patients with diabetes are also 40% more likely than individuals without diabetes to develop glaucoma (NIDDK, 2015). Glaucoma occurs when pressure that builds up in the eye pinches the vessels that supply blood to the retina and optic nerve. The decrease in blood supply damages the retina and optic nerve, leading to loss of vision.

Patients with diabetes are also 60% more likely than those without diabetes to develop cataracts. This clouding of the eye lens also occurs at younger ages in diabetic patients (NIDDK, 2015).

**SYMPTOMS OF EYE COMPLICATIONS**

- Blurry vision
- Difficulty reading signs or books
- Double vision
- Pain in one or both eyes
- Eye redness
- Feeling of pressure in the eye
- Seeing spots or “floaters”
• Straight lines appearing as not straight
• Disrupted peripheral vision

CHRONIC COMPLICATIONS IN CHILDHOOD

T1DM has also been associated with learning difficulties among children. This effect may be due to severe or repeated episodes of hypoglycemia, which may have negative effects on brain development, learning, and memory, particularly among younger children. Chronic hyperglycemia may also have a role in causing cognitive dysfunction, as children with a history of DKA have been shown in clinical studies to have lower rates of accurate memory on structured tasks than those without a history of DKA (Levitsky & Misra, 2016).

Poor glycemic control in children and adolescents is also associated with reduced joint mobility, primarily affecting the hands and feet, and with menstrual irregularities and fingernail changes (paronychia). In addition, slower rates of bone calcium deposition and decreased bone mineral content have been noted among children and adolescents with T1DM compared to healthy children (Gerrits et al., 2015; Levitsky & Misra, 2016).

Patient and Family Teaching and Follow-Up

Patient and family teaching and follow-up are critically important parts of successful treatment of the patient with T1DM. Success is enhanced by a multidisciplinary team approach to teaching the patient and family and supporting them during ongoing, long-term follow-up.

Initial teaching is typically provided by nurses, physicians, and diabetes educators, with additional education about lifestyle modification and health promotion provided as needed by physical therapists, occupational therapists, and others.

Physical therapists may, for example, prescribe and tailor an appropriate therapeutic exercise program, instruct patients with peripheral neuropathy to optimize mobility safety, and address issues of impaired balance and proprioception (Song et al., 2011, Galassetti et al., 2013; Quirk et al., 2014).

Occupational therapists instruct patients in how to optimize day-to-day activities such as organizing and tracking medications; using low-vision and nonvisual devices to draw up and measure insulin doses; and incorporating protective techniques and compensating for peripheral sensory loss in activities that involve the use of hot, cold, or sharp objects.

In addition, meal planning is typically taught to the patient and family by a dietitian and foot care provided, if needed, by a podiatrist. A psychologist, family therapist, or social worker may be involved in the patient’s care to provide psychosocial support and to treat accompanying psychological conditions (e.g., depression and anxiety), if present. Dental professionals and optometrists provide essential information about dental and eye health at annual visits, while
medical specialists (e.g., cardiologists, neurologists, and ophthalmologists) provide additional patient and family care and teaching if complications of T1DM develop over time.

Patient and family teaching regarding T1DM is provided to the patient and family initially at the time of the patient’s diagnosis then reinforced at follow-up visits. It should include the following:

- What diabetes mellitus is
- Carbohydrate counting and the patient’s diet
- Checking the patient’s blood sugar level
- Giving insulin
- Maintaining target blood sugar levels
- Managing illness and infections
- Regular physical exams with clinicians
- A1C testing
- What is involved in staying healthy
- Managing diabetes in school/at work
- Preventing long-term complications

Diet

Diet is one of the first and major steps addressed when developing a strategy to manage T1DM. Maintaining a healthy diet is a crucial part of management of blood glucose levels for the patient with T1DM, but contrary to general belief, there is not a specific “diabetic diet” followed by all patients with T1DM. Instead, patients are encouraged to maintain healthy eating habits, choosing foods that are high in nutritional value but low in sugar, carbohydrates, and sodium. Because patients with T1DM are at an increased risk for cardiovascular complications, a diet low in cholesterol is also recommended (ADA, 2015b; Krans, 2016; NIDDK, 2014b).

Patients’ preferred eating habits and lifestyle should be carefully taken into consideration when designing a diet plan for those with T1DM. This plan should include a recommended daily caloric intake based on the age and physical activity level of the patient as well as guidance for how these calories should be divided throughout the day. For example, one recommended distribution consists of 20% of calories consumed at breakfast, 35% consumed at lunch, 30% consumed at dinner, and 15% consumed in a late-evening snack. However, smaller, more frequent meals throughout the day may be needed for patients who are very physically active or who experience frequent hypoglycemia.
Patients with T1DM often require frequent food intake in combination with insulin therapy to maintain normal blood glucose levels. (Source: NIDDK, 2014b.)

Patient education is an important component in planning and implementing a diet plan. To gain the most from their diet plan, patients need to understand the importance of timing, meal size, and meal frequency in addition to what foods their meals should include.

A dietitian or diabetes educator can help patients learn how to plan meals as well as how to count the amount of carbohydrates they consume in a specific meal. This is necessary to calculate the proper amount of insulin to administer in order to metabolize the carbohydrates in each meal and maintain normal blood glucose levels.

Additionally, a dietitian or diabetes educator can help recommend the amount of fats and protein that should be consumed by the patient. The amount of these nutrients should be individualized depending on the needs of the patient; for example, reduced protein intake is indicated in the case of a patient with a complication such as nephropathy.

*(See also “Resources” at the end of this course.*)
Physical Activity

In addition to diet, exercise is one of the cornerstones of a comprehensive program for the management of T1DM. Patients should therefore be encouraged to maintain a regular exercise routine, including aerobic exercise lasting 30 minutes, three to five times per week (NIDDK, 2014b). Exercise should be undertaken only with approval of the patient’s physician and under the supervision of a physical therapist or exercise physiologist, and may include strengthening exercises such as weight training and stretching exercises such as yoga. Findings from a small clinical trial show that patients with T1DM who have peripheral neuropathy can safely perform both weight-bearing and non-weight-bearing exercise as part of an exercise program (Mueller et al., 2013).

Because exercise can dramatically affect blood glucose levels, patients should be cautioned to take action to prevent hypoglycemia from occurring during exercise. For example, patients may decrease the amount of insulin administered by 10% to 20% or increase their blood glucose level by eating a small snack. Patients can be educated to check their blood glucose levels more often when first beginning an exercise regimen in order to determine how that physical activity will affect their blood glucose levels.

Managing Blood Glucose Levels

It is important for patients with T1DM to maintain normal blood glucose levels. Achieving and maintaining glycemic control is associated with reductions in the frequency and severity of diabetes-related complications. Two primary techniques are currently available to health providers and patients to assess the effectiveness of diabetic management plans on glycemic control: patient self-monitoring of blood glucose (SMBG) and A1C monitoring.

SELF-MONITORING OF BLOOD GLUCOSE

Patients with T1DM should frequently monitor their blood glucose levels, as this can be used to determine whether their disease is being properly treated. SMBG allows patients to evaluate their individual response to therapy and assess whether glycemic targets are being achieved on a daily basis. Results of SMBG can be useful in preventing hypoglycemia and adjusting medications (particularly preprandial insulin doses) and physical activity to maintain blood glucose at desired levels.

Computerized blood glucose meters provide the most accurate and precise measure of the amount of glucose circulating within the blood at a particular time. Because improper use of these meters is the primary cause of their inaccuracy, patients must be educated on how to use them.

Patients receiving multiple-dose insulin or insulin pump therapy should perform SMBG at least prior to meals and snacks, occasionally after meals, at bedtime, and prior to exercise. They should also perform SMBG if they suspect hypoglycemia and afterward until they are normoglycemic.
**A1C TESTING**

In conditions of hyperglycemia, excess glucose enters the red blood cells circulating throughout the blood. Red blood cells also contain hemoglobin, the protein responsible for oxygen transport within the blood. When glucose enters the red blood cell, it links to the hemoglobin protein molecules, forming glycosylated hemoglobin, or A1C. As glucose levels increase, the amount of glycosylated hemoglobin also increases.

The A1C test is a measure of the percentage of hemoglobin molecules that have glucose molecules attached. The A1C level is reflective of the average blood glucose level in an individual over the previous two to three months. Therefore, it is considered a long-term assessment of glucose control. The A1C test can help to manage T1DM by confirming blood glucose self-tests and to judge if a treatment plan is effective.

Because A1C reflects average glycemia over several months and has strong predictive value for diabetes complications, A1C testing should be performed at initial assessment in all patients with T1DM and then as part of continuing care. A1C testing is performed at least twice a year for patients who are meeting treatment goals (i.e., who have stable glycemic control), and every two to three months for patients whose therapy has been changed or who are not meeting their glycemic goals.

**ESTIMATED AVERAGE GLUCOSE (eAG)**

The estimated average glucose (eAG) is a method for understanding the management of diabetes. Estimated average glucose is determined by converting the A1C percentage to mg/dL units. Because these units are the same as those used on blood glucose meters, they are considered to be more familiar to patients with diabetes. Therefore, providing the A1C percentage in these units may help patients to better understand how effectively their T1DM is being controlled.

**Insulin Therapy**

Because T1DM is a disease caused by a loss of the ability to produce insulin, the primary treatment is insulin therapy. In addition, other medications may be prescribed to work in conjunction with insulin in an effort to reduce hyperglycemia. Patients who develop diabetes-related complications often require medication specific to their complication. For example, patients with cardiac complications may be treated with low-dose aspirin therapy, cholesterol-lowering drugs, or high blood pressure medications.

According to current ADA recommendations, most people with T1DM should be treated with multidose insulin injections (3 to 4 injections per day of basal and preprandial insulin) or continuous subcutaneous insulin infusions (via insulin pump) to manage blood glucose levels. In addition, people with T1DM should be taught how to match preprandial insulin doses to planned carbohydrate intake, premeal blood glucose, and anticipated activity levels to help maintain target blood glucose levels.
DOSAGE

In adults, the initial daily dose of insulin is calculated based on the weight of the patient. Because it is quickly degraded, insulin must be administered throughout the day to maintain steady levels, with doses frequently adjusted based on self-monitoring of blood glucose levels. Insulin therapy is typically accomplished by giving a basal insulin in combination with preprandial insulin doses. The basal insulin is either a long-acting (glargine or detemir) or intermediate-acting (NPH) insulin, and the preprandial insulin is either rapid-acting (lispro, aspart, or glulisine) or short-acting (regular) insulin.

Common **insulin regimens** include (Khardori, 2015):

- Split or mixed regimen: NPH plus rapid-acting or regular insulin before breakfast and the evening meal
- Split or mixed variant regimen: NPH with rapid-acting or regular insulin before breakfast, rapid-acting or regular insulin before the evening meal, with NPH before bedtime (to reduce fasting hyperglycemia)
- Multiple daily injections (MDI): A long-acting insulin once daily in the morning or evening (given twice daily in some patients), plus a rapid-acting insulin before meals and snacks (dose adjusted based on blood glucose level)
- Continuous subcutaneous insulin infusion (CSII): Rapid-acting insulin infused continuously through and insulin pump at one or more basal rates, with additional short-acting insulin given if blood glucose levels exceed target levels

ADMINISTRATION

Several different types and formulations of human insulin are available to treat T1DM. An inhaled formulation of insulin was previously available but discontinued in 2007 due to too little use by patients. Oral administration of insulin is not possible, because the enzymes in the stomach create too harsh an environment and lead to insulin degradation. Therefore, the only currently available options for insulin therapy are subcutaneous injection or intravenous administration.

Subcutaneously injected insulin is the first-line therapy. Insulin injections are self-administered using either a needle and syringe or an insulin pen—a device that resembles an ink pen, with the “ink” cartridge instead filled with insulin.

Insulin may also be administered via a battery-operated infusion pump. Generally, this method is used to subcutaneously deliver a continuous amount of rapid-acting insulin through a catheter. The steady-state amount of insulin that results is referred to as the patient’s “basal level.” Prior to each meal, the patient must still test their blood glucose level and self-inject additional insulin as needed. This method allows better control of blood glucose levels than relying only on self-injecting insulin multiple times per day. Disadvantages of the use of insulin infusion pumps
include increased risk for weight gain, increased expense compared to multidose insulin injections, and inconvenience associated with wearing the insulin pump most of the time.

**TYPES OF INSULIN**

Types of insulin are categorized based on their time of onset, peak, and duration of action. Rapid-, short-, intermediate-, and long-acting insulin preparations are available for use in the United States. Various pork, beef, and beef-pork combination insulins were previously widely available, however, recombinant human insulin is now used almost exclusively. Commercially prepared insulin mixtures are also available (ADA, 2015a; Khardori, 2015).

<table>
<thead>
<tr>
<th>TYPES OF INSULIN</th>
<th>Name</th>
<th>Onset (hours)</th>
<th>Peak (hours)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid- and Short-Acting</strong></td>
<td>Glulisine insulin</td>
<td>0.25</td>
<td>0.5–1.5</td>
<td>3–5</td>
</tr>
<tr>
<td></td>
<td>Lispro insulin</td>
<td>0.25</td>
<td>1–3</td>
<td>1–5</td>
</tr>
<tr>
<td></td>
<td>Aspart insulin</td>
<td>0.25</td>
<td>1–3</td>
<td>1–5</td>
</tr>
<tr>
<td></td>
<td>Regular insulin</td>
<td>0.5–1</td>
<td>2.5–5</td>
<td>4–12</td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td>Neutral protamine Hagedorn (NPH)</td>
<td>1–2</td>
<td>4–12</td>
<td>12–18</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td>Insulin detemir</td>
<td>1</td>
<td>stable levels (no peak)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Insulin glargine</td>
<td>1–2</td>
<td>stable levels (no peak)</td>
<td>24</td>
</tr>
</tbody>
</table>

Sources: ADA, 2015a; Khardori, 2015.

Insulin therapy regimens for patients with T1DM frequently combine insulin types, offering patients the ability to benefit from each class. This is commonly done by drawing calculated doses of two insulin types into the same syringe, allowing for a single injection. This method should only be done immediately before administering the insulin injection. Premixed insulin preparations are also available, but their fixed ratios of each insulin type may limit their use.

**Rapid-Acting and Short-Acting**

Rapid-acting and short-acting insulins include lispro insulin, aspart insulin, glulisine insulin, and regular insulin. These are the only available insulins that can be administered intravenously. Because of their rapid onset of action, they can be used when quick control of blood glucose levels is needed, such as before a meal. A rapid influx of insulin stimulates glucose uptake and storage, reducing blood sugar.
Regular (traditional) insulin is a formulation of zinc insulin crystals suspended in solution. The onset of action for traditional insulin is between 0.5 to 1 hour, with a peak activity between 2.5 and 5 hours following administration. The duration of activity of regular insulin is 4 to 12 hours.

The other rapid-acting insulins are genetically engineered versions of regular insulin in which specific amino acid substitutions have been made. Lispro insulin contains a reversal of the amino acids lysine and proline, while aspart insulin contains an aspartic acid substitution for proline. Each of these modifications has the result of allowing more rapid insulin absorption and activity, with a rapid onset (up to 15 minutes), peak activity (1 to 3 hours), and duration (between 1 to 5 hours) of action. These quicker responses allow the patient greater flexibility in administration, with the possibility of their administration immediately before eating.

**Intermediate-Acting**

Intermediate-acting insulins have a slower onset of action compared to rapid-acting formulations but have a characteristically longer duration of action. Thus, they are often administered in combination with rapid-acting formulations, which maximizes the benefit of both insulin types. Additionally, intermediate-acting insulin formulations are often used at bedtime in order to provide needed insulin throughout the night.

Neutral protamine Hagedorn (NPH) is a suspension of zinc insulin crystals combined with protamine, a positively charged amino acid polypeptide. The onset of action of this class of insulins is between 1 and 2 hours, with a peak effect occurring in 4 to 12 hours. The greatest benefit of intermediate-acting insulins is their long duration of activity, up to 24 hours.

**Long-Acting**

Long-acting insulins, as their name suggests, have a very long duration of action. This insulin class is generally combined with rapid-acting insulin, offering patients an improved and steadier control of their insulin and blood glucose levels. Long-acting formulations are often administered in the morning in order to provide all-day insulin coverage. The pharmacology of long-acting insulin is similar to that of the natural insulin normally secreted by the pancreas. These insulins are generally administered once daily.

Some clinical studies have reported a possible association of insulin glargine with cancer (Rendell et al., 2013; Wu et al., 2016). The data within these studies must be carefully compared and interpreted, as they are inconsistent between studies, derived from patient populations with different baseline characteristics, and generated from studies conducted over too short a time period to allow this conclusion to be made. The American Diabetes Association cautions against overreacting to these reports.
Amylin Therapy

Amylin is a small hormone that is normally secreted by pancreatic beta cells in conjunction with insulin. Once it enters the blood circulation, amylin contributes to glycemic control by delaying gastric emptying, decreasing blood glucose release following a meal, and modulating appetite. These mechanisms allow amylin to work synergistically with insulin to keep blood glucose levels normal.

A synthetic version of amylin, called pramlintide (Symlin), is available. Pramlintide is currently approved for use in adult patients with T1DM who are unable to achieve a desired glucose level despite optimal insulin therapy. It is subcutaneously administered prior to a meal. Initially started at a low dose (15 mcg), if the patient does not experience significant nausea, the pramlintide dosage is gradually titrated upward in 15 mcg increments to a final maintenance dosage between 30 and 60 mcg per dose.

When initiating pramlintide, the patient should decrease their normal insulin dosage. Once the final pramlintide dose has been determined, the patient can then adjust their insulin dosage to optimize blood glucose control (Mayo Clinic, 2015b).

Treating Hyperglycemia

Hyperglycemia, the hallmark clinical sign of T1DM, occurs when an individual experiences levels of blood glucose above target levels. Nearly all patients with T1DM experience hyperglycemia during the course of their disease. In patients with T1DM, hyperglycemia may be indicative of poor disease management. This may occur as a result of a skipped or forgotten dose of insulin, too low a dosage of insulin, eating too much food, or eating foods that add too much sugar to the diet. Other causes of hyperglycemia in patients with T1DM include infection, illness (such as a cold or flu), increased stress, or decreased physical activity (WebMD, 2015).

Hyperglycemia can be treated by changes in exercise, diet, and/or alterations to the patient’s insulin regimen. Patients can often lower their blood glucose levels sufficiently by making changes in diet or by exercise alone. It is essential, however, that patients do not exercise if they have blood glucose levels ≥240 mg/dL and ketones are present in their urine, as exercising under these conditions can drive blood glucose levels even higher. Patients experiencing chronic hyperglycemia can require changes in the amount, timing, or type of insulin they receive each day (WebMD, 2015).

SYMPTOMS OF HYPERGLYCEMIA

- Increased thirst
- Blurred vision
- Frequent urination
- Increased hunger
- Numbness or tingling in the hands and feet
- Fatigue
Patient Adherence to Therapy

Patient nonadherence to type 1 diabetes treatment is an issue of considerable concern and is especially common among adolescent and young adult patients. A nonjudgmental, holistic approach to patient and family teaching that promotes positive family interactions (e.g., interventions focused on increasing parent-child communication about T1DM treatment) have been shown in clinical studies to be associated with better adherence as reflected in enhanced glycemic control in pediatric and adolescent patients (Hood et al., 2010).

It is important to note that depression occurs frequently among patients with T1DM and may be a cause of nonadherence in many patients (NIMH, 2015). Because of this common correlation, chronically nonadherent patients should be evaluated for the presence of undiagnosed or undertreated depression and treated as necessary to promote optimal adherence to treatment. Depression most often occurs within one year of diagnosis of T1DM.

CASE

A 14-year-old boy, diagnosed with T1DM one year ago, has been hospitalized three times in the intervening months for DKA. His blood sugars have fluctuated greatly, and he has reported feeling shaky in the middle of the night on occasion. He does not like to check his blood sugar and often finds himself feeling “sick” between meals. The patient complains that checking his blood sugar at school makes him feel “weird,” and he “just wants to be a normal kid.”

Social service interviews with the family reveal that the boy was also diagnosed with depression six weeks ago but that he does not routinely take his antidepressant medication. He also does not take his insulin without close supervision by his parents, who report that they often have to argue with him about his need to take his insulin doses. It had been suggested that the patient attend a summer camp for youth with diabetes, where he could meet other teenagers coping with the disease, but so far he has refused to go.

The patient is currently admitted for another episode of DKA. He states that he hates being diabetic, is very depressed about it, and is considering trying to kill himself because of these depressed feelings. After he is medically stabilized following the DKA episode, the patient is transferred to the psychiatric ward of the hospital for observation and treatment for suicidality and severe depression.

**Question:** How can the patient’s treatment for depression assist in promoting his adherence with his treatment program for T1DM, and what resources are available to him and his family?

**Answer:** Depression can be a reaction to stress and changes in routine that occur because of the T1DM diagnosis and the demands and responsibilities required by its treatment. Apathy associated with depression can interfere with a patient’s ability to handle these demands and responsibilities. Because of the lifelong nature of T1DM, patients with the disease must contend with these demands and responsibilities on an ongoing basis, which may require long-term emotional support in the form of personal and family counseling to promote optimal motivation and adherence to their plan of care.
After his initial psychiatric hospitalization and stabilization for depression, a teenaged patient such as this one who is having trouble accepting his diagnosis may benefit from individual and family counseling, from being involved in a peer support group, and from short- or long-term antidepressant medication therapy. In addition, the patient and his family may benefit from the support of agencies such as the Starlight Children’s Foundation (see “Resources” at the end of this course), which are dedicated to creating projects that help children and teens address psychosocial challenges that accompany chronic illnesses.

EMERGING THERAPIES

Prevention and Reversal Strategies

Several prevention and reversal strategies for immune-mediated T1DM are currently being evaluated in clinical studies. These approaches include the use of immunomodulating agents, including the use of insulin therapy in the prediabetic period. Other interventions being explored in clinical studies include use of the dietary supplements nicotinamide and anti-CD3 antibodies (i.e., monoclonal antibodies that exert immunosuppressive action by binding to CD3 receptors on the surface of T cells), which may protect beta cells from autoimmune injury (Gale, 2014).

Transplantation Procedures

Transplantation of islet cells and whole pancreases has been performed with the goal of ending patients’ dependence on exogenous insulin. Transplantation of islet cells is performed by isolating islet cells from donor pancreases then injecting the cells directly into a major vein in a patient’s liver. The islet cells are then carried to capillaries in the liver, where they produce insulin.

In addition, whole pancreas transplants and double transplants of pancreases and kidneys have shown favorable long-term success rates for some patients with T1DM. Transplantation of splenocytes has, in addition, been shown to give rise to new islet cells in patients whose underlying autoimmune disease is controlled.

Drawbacks of these procedures are that immunosuppressant agents are required for the patient’s lifetime so that his or her body does not reject the foreign islet cells or transplanted tissue. In addition, two or more donor pancreases are necessary to supply sufficient pancreatic tissue for one patient. Unfortunately, with the currently limited supply of donor pancreases, this requirement makes these procedures feasible for only 1% of patients.

Researchers are currently examining alternative approaches to the transplantation of islet cells, including the use of umbilical cord cells, embryonic or adult stem cells, bone marrow transplantation, and other types of cellular therapies to help patients with T1DM reduce their dependence on exogenous insulin (Dholakia et al., 2016; Lysy et al., 2016; Matsumoto et al., 2016; Rekittke et al., 2016).
CONCLUSION

Type 1 diabetes mellitus is a serious disease whose chronic nature requires a lifelong commitment to therapy. Unlike T2DM, T1DM is caused by an autoimmune reaction, the results of which cause the body to be unable to properly store and process blood glucose. The hallmark clinical sign of T1DM is hyperglycemia. Symptoms of hyperglycemia include increased thirst, blurred vision, frequent urination, and increased hunger.

While there are many strategies to manage T1DM, such as exercise and diet, the primary treatment is insulin therapy to make up for the lack of insulin production in these patients. Insulin administration allows patients to normalize their blood glucose levels. Tight control of blood glucose is an essential step to prevent the development and/or worsening of diabetes-related complications, a common occurrence in these patients.

The long-term therapy of patients with T1DM is best managed by a multidisciplinary care team comprised of primary care providers, nurses, endocrinologists, and other specialists (i.e., cardiologists, ophthalmologists, dermatologists, podiatrists, physical therapists, occupational therapists, registered dietitians, and diabetes educators). Although there is currently no cure, with continued care and oversight as well as careful and committed adherence to lifestyle changes and treatments, patients with T1DM may experience an active and full life.

RESOURCES

American Diabetes Association
http://www.diabetes.org

Basics about diabetes (CDC)

Children with diabetes (Online community for kids, families, and adults with diabetes)
http://www.childrenwithdiabetes.com

Diabetes (Mayo Clinic)
http://www.mayoclinic.com/health/diabetes/DS01121

Diabetes A–Z (NIDDK)
http://www.niddk.nih.gov/health-information/health-topics/diabetes/Pages/default.aspx

Diabetes type 1 (Medline Plus)
Exercise and type 1 diabetes (ADA)

International Diabetes Federation
http://www.idf.org

Meal planning for children with type 1 diabetes

Planning meals (ADA)

Type 1 diabetes and exercise
http://www.endocrineweb.com/conditions/type-1-diabetes/type-1-diabetes-exercise

REFERENCES


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TEST

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1. Which description does the clinician use to explain type 1 diabetes (T1DM) to a patient who was recently diagnosed with the disease?
   a. T1DM is a disease in which the beta cells of the pancreas produce little to no insulin, so the blood sugar levels can become too low.
   b. T1DM is a disease in which the body no longer makes enough insulin to keep the blood sugar levels normal, so the blood sugar levels can become too high.
   c. T1DM is a disease in which there is an alteration in the secretion of insulin, so the blood sugar levels can become too low.
   d. T1DM is a disease in which the body makes too much insulin to keep the blood sugar levels normal, so the blood sugar levels can become too high.

2. What percentage of all cases of diabetes among U.S. adults is attributed to type 1 diabetes?
   a. 5% to 10%
   b. 11% to 16%
   c. 20% to 25%
   d. 30% to 40%

3. When a 25-year-old male patient asks what has caused him to develop type 1 diabetes (T1DM), his clinician responds that:
   a. His body’s cells have become resistant to the effects of insulin, causing his blood sugar levels to rise.
   b. T1DM is a non-progressive disease with self-limiting effects caused by a bacterial infection.
   c. The most likely cause is an autoimmune reaction against his pancreatic islet cells, resulting in little to no insulin production.
   d. The exact cause is unknown, but the disease appears most often among patients who are older than 55 years of age.

4. A 28-year-old woman who was diagnosed with type 1 diabetes (T1DM) at 18 years of age is pregnant with her first child. During an obstetric visit, she asks her clinician how she can reduce her baby’s risk for T1DM. The clinician explains that T1DM cannot currently be prevented, but she can reduce her baby’s risk by:
   a. Breastfeeding her baby for at least one year.
   b. Arranging for the baby to receive immunotherapy.
   c. Giving the baby calcium supplements beginning at 1 month of age.
   d. Placing the baby on a low-fat diet at 6 months of age.
5. Which is considered to be a possible risk factor for developing type 1 diabetes?
   a. Being overweight or obese
   b. Recurrent kidney infections
   c. Exposure to viruses
   d. Lack of physical exercise

6. The hallmark clinical sign of type 1 diabetes is:
   a. Urticaria.
   b. Iritis.
   c. Hyperglycemia.
   d. Hypoglycemia.

7. Which test is used to help monitor the long-term control of blood glucose levels in patients with type 1 diabetes?
   a. A random plasma glucose test
   b. An oral glucose tolerance test
   c. A fasting plasma glucose test
   d. An A1C test

8. A 24-year-old woman who was recently diagnosed with diabetes undergoes additional testing to determine whether she has type 1 diabetes or type 2 diabetes. To differentiate between the two conditions, the clinician orders which test?
   a. A C-peptide test
   b. A random plasma glucose test
   c. An oral glucose tolerance test
   d. An A1C test

9. An acute complication of type 1 diabetes is:
   a. Diabetic ketoacidosis.
   b. Nephropathy.
   c. Pulmonary infection.
   d. Hypertension.
10. Patients with type 1 diabetes who begin to experience symptoms of hypoglycemia are instructed to:
   a. Eat a “quick-fix” food and monitor blood glucose levels every 15 minutes until they are normoglycemic.
   b. Eat a “quick-fix” food, then wait to feel better to determine whether their symptoms are due to hypoglycemia.
   c. Contact their healthcare provider to ask for guidance before any intervention.
   d. Immediately sit down to rest and drink plenty of water.

11. A potential chronic complication of type 1 diabetes is:
    a. Chronic obstructive pulmonary disease.
    b. Osteoporosis.
    c. Mitral valve prolapse.
    d. Retinopathy.

12. A 14-year-old boy with type 1 diabetes (T1DM) for one year develops learning problems related to difficulty remembering things in class. When his parents ask whether this could be caused by his T1DM, the clinician responds:
    a. “Yes, learning difficulties can be caused by T1DM and may be related to either repeat hypoglycemic or hyperglycemic episodes.”
    b. “Yes, learning-related difficulties associated with T1DM have been linked to the development of hypertension.”
    c. “Yes, learning-related difficulties with T1DM are predominantly caused by altered sensory function from diabetic peripheral neuropathy.”
    d. “No, learning difficulties are not chronic complications associated with T1DM.”

13. The most effective management of care for patients with type 1 diabetes is achieved by implementing a:
    a. Multidisciplinary team approach.
    b. Family psychotherapy approach.
    c. Surgical consultation.
    d. Social work consultation.

14. The onset of action of regular insulin is:
    a. 0.5 to 1 hour.
    b. 1.25 to 1.5 hours.
    c. 4 to 8 hours.
    d. 9 to 12 hours.
15. The onset of action of intermediate-acting insulin is:
   a. 0.5 to 0.75 hour.
   b. 1 to 2 hours.
   c. 4 to 8 hours.
   d. 9 to 12 hours.

16. The onset of action of long-acting insulin glargine is:
   a. 0.5 to 1 hour.
   b. 1 to 2 hours.
   c. 4 to 8 hours.
   d. 9 to 12 hours.

17. A 26-year-old male patient, who is a marathon runner, is newly diagnosed with T1DM. The clinician explains that the patient can use exercise to help treat hyperglycemic episodes only if he has no ketones in his urine and his blood sugar level is less than:
   a. 240 mg/dL.
   b. 250 mg/dL.
   c. 260 mg/dL.
   d. 270 mg/dL.

18. Which symptom is not typically associated with hyperglycemia?
   a. Thirstiness
   b. Headache
   c. Blurred vision
   d. Fatigue

19. A 14-year-old female adolescent with type1 diabetes, who is hospitalized for more frequent hyperglycemic episodes, is diagnosed with diabetic ketoacidosis. During discharge teaching, the nurse notes that the patient reports sometimes skipping her insulin doses at home and the patient appears generally withdrawn and sad. The nurse suspects that the patient’s nonadherence to insulin therapy may be related to:
   a. Anorexia nervosa.
   b. Anxiety.
   c. Recreational drug use.
   d. Depression.
20. Emerging medical therapies for T1DM include:
   a. Pancreas transplants.
   b. Liver transplants.
   c. Acupuncture.
   d. Desensitization therapy.