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Type 1 Diabetes Mellitus

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Practice Gaps

1. All children with type 1 diabetes mellitus (T1DM) should have their blood sugar managed with basal-bolus insulin treatment by either multiple daily injections or an insulin pump.
2. All children with T1DM should have access to a pediatric endocrinologist with a diabetes management team with resources to support patients and families.
3. All children with T1DM should be monitored for symptoms and/or screened for commonly associated conditions such as thyroid and celiac disease.

Objectives   After completing this article, readers should be able to:

1. Recognize the presenting signs and symptoms of type 1 diabetes mellitus (T1DM).
2. Know the key principles of effective diabetes self-management and the diabetes care team's role in facilitating effective self-management.
3. Know the acute and chronic complications of (T1DM).
4. Identify how different categories of insulin analogues are used in daily insulin regimens.

True, it is a fight, but there is pleasure in the struggle. Victory comes to the courageous; and without courage and common sense, success awaits no one. I look upon the diabetic as charioteer and his chariot as drawn by three steeds named Diet, Insulin, and Exercise. It takes skill to drive one horse, intelligence to manage a team of two, but a man must be a very good teamster who can get all three to pull together.

EP Joslin, 1933

Introduction

Type 1 diabetes mellitus (T1DM) is a disorder of glucose homeostasis characterized by autoimmune destruction of the insulin-producing pancreatic β-cell that progressively leads to insulin deficiency and resultant hyperglycemia. If left untreated, insulin deficiency leads to progressive metabolic derangement, with worsening hyperglycemia, ketoacidosis, starvation, and death. In an effort to restore and maintain euglycemia, treatment attempts to mimic the action of the native β-cell by exogenously replacing insulin and includes frequent monitoring of blood glucose levels.

As the visionary pioneer Dr. Elliott P. Joslin believed, the best possible outcomes of T1DM treatment are realized when a sense of empowerment, rather than victimization, is imparted to both patient and family. Achieving this empowerment through diligence and education enables an individual living with T1DM to attain optimal health and

Abbreviations:

ADA:	American Diabetes Association
DKA:	diabetic ketoacidosis
HbA1c:	glycosylated hemoglobin
I:C ratio:	insulin-to-carbohydrate ratio
IV:	intravenous
TDD:	total daily dose
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus

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well-being and constitutes the ultimate goal—and challenge—of the medical team.

The epidemiology and pathophysiology of T1DM are discussed in this article, followed by a practical review of the diagnosis and treatment of this chronic, lifelong condition emphasizing the goal of effective diabetes self-management as leading towards enduring wellness.

Epidemiology

The prevalence of T1DM among patients younger than age 20 years in the United States is estimated at 1.54 cases per 1,000 youth. (1) The highest prevalence is seen among non-Hispanic white children, with 2.0 cases per 1,000, which is 50% higher than that of black children (1.34 cases per 1,000) and double that of Hispanic children (1.0 cases per 1,000). (1) Girls and boys are almost equally affected, a fact that distinguishes T1DM from most autoimmune illnesses, which tend to affect females more frequently.

The incidence of T1DM in the US pediatric population is estimated to be 19.0 cases per 100,000 person-years. The highest incidence is in non-Hispanic white children followed by black and Hispanic children (23.8, 14.2, and 13.7 cases per 100,000 person-years, respectively). (2) The peak age of onset in the United States appears to occur in early puberty to midpuberty. In most studies, a seasonal variation in onset has been observed in children, with the highest incidence of T1DM occurring during the winter months and the lowest occurring during the summer months. This finding may result from winter months having higher rates of viral infections, which cause a metabolic stress that exceeds the ability of the residual β-cell mass to produce insulin sufficient to maintain euglycemia. Interestingly, the incidence rate of T1DM appears to be increasing in the United States each year, with a mean annual increase in incidence of 2.3% per year, consistent with a rising trend observed globally of 2.8% per year. (3–5)

Pathogenesis

A predisposition for T1DM begins at birth with the inheritance of genetic risk factors. Although most newly diagnosed patients have no family history of T1DM, unaffected children who have a relative with T1DM are at increased risk as compared to the general population. The most strongly associated susceptibility genes for T1DM are located in the major histocompatibility complex region on chromosome 6 and most likely operate by directing immune development and permitting presentation of autoantigens to autoreactive lymphocytes.

A triggering environmental factor probably plays an additional role in evoking clinical disease. This hypothesis is supported by the fact that monozygotic twins are not uniformly concordant for disease progression. Environmental factors such as infection may contribute to autoimmune activation by inciting cross-reactivity against antigens on the β-cell that bear a similar molecular structure or in a non-specific way, such as promoting the production of proinflammatory cytokines that injure islet tissue.

The progression from immune activation to clinically relevant islet cell loss may take many years and is marked early by the presence of serum autoantibodies. Once the β-cell mass is insufficient to maintain euglycemia, clinical symptoms evolve.

Clinical Presentation

New-onset T1DM usually presents in one of three ways: with "classic" presenting symptoms, with diabetic ketoacidosis (DKA), or more rarely, as an incidental finding.

Classic Symptoms

New-onset T1DM presents in the majority of pediatric patients with the classic symptoms of polyuria and polydipsia (69%) and somewhat less frequently with polyphagia and weight loss (33%). (6) Patients and families usually report the duration of symptoms as lasting 1 to 2 weeks, but sometimes several months. Often, these symptoms become more apparent after an episode of enuresis or with the emergence of nocturia. Patients frequently have vague complaints, such as fatigue, and may note blurred vision.

Diabetic Ketoacidosis

In roughly one-quarter of cases, a patient with new-onset T1DM will present with DKA. These children and adolescents tend initially to have the same classic symptoms (polyuria, polydipsia, polyphagia, weight loss), which become more severe. As acidosis develops, these patients frequently lose their appetite and nausea, vomiting, and abdominal pain become the significant symptoms. To compensate for the worsening ketoacidosis, hyperpnea develops (Kussmaul respirations). If unchecked, neurologic status progressively deteriorates as acidosis and hyperosmolality worsen, and the patient progresses from drowsiness to lethargy to obtundation. Risk factors associated with an initial presentation of DKA include younger age, especially children younger than age 2 years, ethnic minority status, and lower socioeconomic and parental education levels.

Incidental Finding

A smaller number of children and adolescents are diagnosed as having diabetes despite having none of the classic symptoms of T1DM. These children usually have

impaired glucose tolerance because of β-cell loss, but have not yet had overt symptoms. As home blood glucose monitoring has become more widespread, family members with diabetes may check blood glucose levels in other family members, and hyperglycemia will be detected despite a lack of symptoms. Families with diabetes concerned about risk in their children should be directed to a T1DM TrialNet website where screening and longitudinal observation can be performed (www.diabetes-trialnet.org). In other situations, children will have a seemingly unrelated presenting complaint (eg, vulvovaginal candidiasis) that leads to the detection of glycosuria and then hyperglycemia caused by T1DM.

Diagnosis

The diagnostic criteria for all forms of diabetes mellitus are outlined in Table 1. In most cases, the clinical history is strongly suggestive of new-onset diabetes, and laboratory evaluation confirms the diagnosis. Once diabetes is diagnosed, it is important to determine which type of diabetes the patient has to form an appropriate treatment regimen. During the initial assessment, it is imperative also to determine whether potential associated acute comorbidities, such as DKA and cerebral edema, are present. At a minimum, initial laboratory studies should include a serum glucose level to establish the degree of hyperglycemia, and a low threshold should be maintained in ill-appearing patients for obtaining serum electrolytes and a blood gas for detecting possible electrolyte abnormalities that must be corrected as well as the presence of DKA.

An increasingly frequent diagnostic dilemma is distinguishing between T1DM and type 2 diabetes mellitus (T2DM) as the incidence of obesity and T2DM in the pediatric population rises. Differentiating between the

two in the obese patient with new-onset diabetes is complicated by presenting characteristics that often overlap. Several features, however, are useful in making a presumptive diagnosis of T1DM versus T2DM in this situation;

- T2DM occurs after pubertal onset in the majority of cases.
- T2DM is associated commonly with obesity, acanthosis nigricans, and features of the metabolic syndrome such as hypertension and dyslipidemia; these features are less common in T1DM.
- Patients with new-onset T1DM are more likely to present with the classic symptoms of new-onset diabetes.
- The presence of autoantibodies associated with T1DM are more suggestive of, but not exclusive to, T1DM than T2DM, particularly when multiple autoantibodies are elevated.
- Patients with new-onset T2DM are approximately five times more likely to have an affected first-degree family member who has T2DM than are patients with new-onset T1DM to have an affected first-degree family member with T1DM.
- The prevalence of T2DM is substantially higher among Native-American, Hispanic, and African-American ethnicities, compared to non-Hispanic white youth.

Patients with new-onset T1DM and T2DM can present with DKA, and the treatment of DKA will be the same. Those patients who present initially in DKA should be continued on insulin until the diagnosis is clear; some patients with T2DM may be able to transition to oral medications once stabilized.

Other causes for new-onset diabetes warrant consideration. These disorders include genetic defects of β-cell function, diseases of the exocrine pancreas, and drug-induced

Table 1. Criteria for Diagnosis of Diabetes

$HbA_{1c} \geq 6.5\%$ (where the test is performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardized to the Diabetes Complications and Control Trial assay)*

OR

Fasting plasma glucose level $\geq$ 126 mg/dL (where fasting is defined as no caloric intake for at least 8 hours)*

OR

2–hour oral glucose tolerance test reading $\geq$ 200 mg/dL (where performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight if weight is <18 kg) *

OR

Random plasma glucose level $\geq$ 200 mg/dL in a patient with classic symptoms of hyperglycemia

Data from American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care.* 2011;34 (Suppl 1):S11-S61. (18)
*In the absence of unequivocal hyperglycemia, the result should be confirmed by repeat testing.
HbA1c: glycated hemoglobin.

effects. Genetic defects in insulin secretion are becoming recognized increasingly. Among these conditions, maturity-onset diabetes of the young (MODY) syndromes are a group of disorders characterized by monogenic defects in β-cell function. These defects limit insulin secretion by the β-cell, which leads to hyperglycemia; but the disease severity tends to be milder. The condition presents before age 25 years, is not associated with elevated autoantibodies, and is transmitted in an autosomal dominant fashion. Diseases that cause damage to the exocrine pancreas can lead to diabetes, most commonly in cystic fibrosis–related diabetes and late in the course of chronic pancreatitis. Additionally, a number of drugs and chemicals are known to induce diabetes, including immunosuppressants such as tacrolimus and cyclosporine, glucocorticoids, and chemotherapeutics such as L-asparaginase.

Treatment

Once the diagnosis of T1DM is established, initial care focuses on restoring euglycemia and teaching the patient and family the basic skills required to take care of diabetes at home. Initial management is influenced by whether the patient is acutely ill at presentation (eg, whether DKA is present). The approach to initial care should also be tailored to the developmental stage of the patient. Ideally, every child newly diagnosed as having T1DM should be evaluated by a diabetes team consisting of a pediatric endocrinologist, nurse educator, dietician, social worker, child life specialist, and mental health professional.

At a minimum, during the initial visit with the diabetes team, the family should learn how to check and record blood glucose concentrations using a home blood glucose meter, how to draw up and deliver insulin using a syringe, and how to detect and treat hypoglycemia. Once initial management is completed, care shifts toward ongoing management. The patient and family, with the support of the diabetes team, progressively assume greater ownership of diabetes care, with the support of the diabetes team. Ultimately, optimal diabetes management seeks to strike a balance between restoring blood glucose into the euglycemic range in order to minimize the microvascular and macrovascular complications associated with chronic hyperglycemia while simultaneously minimizing a child's unique vulnerability to hypoglycemia.

Initial Insulin Regimen

Insulin therapy is prescribed to mimic the action of the β-cell by achieving three basic goals:

1. *Facilitate metabolism and storage of consumed food.* During feeding, insulin is needed to facilitate transport of glucose from blood into the cells of insulin-dependent tissues such as muscle, fat, and the liver. In the physiologic state, insulin is secreted almost immediately upon eating. By contrast, insulin therapy in T1DM utilizes subcutaneous delivery of rapid or short-acting insulin with meals and snacks. Usually, the dosage of insulin given is proportional to the amount of carbohydrates being ingested. For example, a patient may take 1 unit of insulin for every 10 grams of carbohydrates being consumed. This insulin-to-carbohydrate (I:C) ratio is titrated frequently during the initial weeks of management, and then routinely during ongoing management. The "Rule of 500" sometimes is used to calculate this initial I:C ratio dose by dividing 500 by the estimated total daily dose (TDD) of insulin (estimation of TDD is discussed below).
2. *Normalize hyperglycemia.* One key to tight glycemic control is to minimize the magnitude and duration of hyperglycemic excursions throughout the day. To accomplish this goal, an additional "correction factor" dose of rapid or short-acting insulin is added to the amount of insulin given to cover carbohydrates at mealtimes. The correction factor dose is proportional to the degree of hyperglycemia. To calculate the initial correction factor dose, many clinicians will utilize the "Rule of 1,800" by dividing 1,800 by the estimated TDD. The number estimates how much 1 unit of insulin should drop the blood glucose concentration. For example, a patient with an estimated total daily dose of 18 units of insulin would be expected to have a 100 mg/dL drop in blood glucose for each unit of insulin delivered. Therefore, if the target blood glucose level is 100 mg/dL, the patient should receive an additional 1 unit for a blood glucose of 200 to 299 mg/dL, 2 units for 300 to 399 mg/dL, 3 units for 400 to 499 mg/dL, and so on as a correction factor dose. As with the I:C ratio dose, the correction factor dose is titrated according to the patient's blood glucose trends.
3. *Maintain euglycemia during fasting.* Because glucose-increasing counter-regulatory hormones retain their ability to stimulate hepatic glucose production, "basal" insulin is needed to maintain a euglycemic balance between meals. For this reason, one or two daily doses of long-acting insulin are given to maintain a low level of insulin during fasting.

When the initial insulin regimen is being designed, it is helpful to approximate the initial TDD of insulin. Children with long-standing diabetes usually require somewhere

between 0.5 and 1.0 units/kg per day of insulin. Prepubertal children tend to require a lower TDD, and pubertal children usually need a higher TDD. In most cases, half of the TDD is given as long-acting insulin and the other half is given as rapid or short-acting insulin to cover meals. With the guidance of the diabetes care team, these doses are adjusted empirically for each patient based on the patient's blood glucose log.

It is also important to be mindful of the "honeymoon" phase that follows initial diagnosis and treatment with insulin. During this time, endogenous insulin secretion from remaining β-cells continues, and in many cases, insulin doses must be lowered to prevent hypoglycemia. The honeymoon phase tends to occur more frequently and lasts longer in those patients who are older and have a milder initial presentation. Usually, the insulin dose reaches its nadir at approximately 3 months into therapy and the honeymoon phase ends by 7 months, although this interval is highly variable. This period offers a great opportunity for achieving tight control, and it has been suggested that tight initial control begets improved long-term control.

Insulin analogues are categorized by their time course of action as rapid, short, intermediate, or long-acting, as outlined in Table 2 and shown in Figure 1. These pharmacodynamic characteristics form the basis of the framework for a daily insulin regimen that seeks to mimic the β-cell. Figure 2 illustrates a "basal–bolus," or "multiple daily injection" regimen, in which rapid-acting insulin is given with meals and snacks and long-acting insulin

to provide a steady amount of insulin with little to no peak between mealtimes. This protocol is the most widely used injection regimen. Short- and intermediate-acting insulin sometimes are utilized in regimens to minimize the number of daily injections. In a "mixed-split" regimen, a short-acting insulin is mixed in the same syringe with an intermediate analogue, and two daily doses are given—one with breakfast and one with dinner. The short-acting insulin covers breakfast and dinner, while the delayed action of the intermediate-acting insulin is utilized to cover lunch and a bedtime snack. A major advantage of the basal–bolus" regimen over the mixed–split regimen is greater flexibility for when meals and snacks can be eaten and how many carbohydrates can be consumed. Good results can be obtained with a mixed-split regimen, but this treatment requires a patient to eat the same amount at the same time each day.

Diabetic Ketoacidosis
Initial Assessment and Monitoring
The biochemical criteria for DKA include a blood glucose level greater than 200 mg/dL and venous pH less than 7.30 or a bicarbonate level less than 15 mmol/L. The severity of DKA can be classified according to the severity of the acidosis, as shown in Table 3. (7,8) Precipitating factors that could lead to the onset of DKA—such as infection, or in the case of patients with known T1DM, insulin omission, insulin pump failure, or failure to match insulin dosing to metabolic requirements during illness—should be investigated. Medication noncompliance is frequently the cause of recurrent DKA. In one study, 85% of hospital admissions for DKA involved discontinuation of medication use. (9) The degree of dehydration should be appraised clinically at presentation and monitored for improvement during treatment. Unfortunately, it is difficult in this setting to estimate dehydration accurately according to the clinical findings more frequently associated with acute dehydration because water losses occur over a longer period of time and are both intracellular and extracellular. The majority of patients who present with DKA are between 5% and 10% dehydrated.

Because all patients who have ketoacidosis do not have DKA, other conditions with similar presentations

Table 2. **Approximate Pharmacodynamic Characteristics of Insulin Analogues**

Insulin analogue	Onset of action	Peak action (h)	Effective duration (h)
Rapid acting			
Lispro (Humalog®, Eli Lilly)	15 min	0.5–1.5	4–6
Aspart (NovoLog®, Novo–Nordisk)			
Glulisine (Apidra®, Sanofi–Aventis)			
Short acting			
Regular	30–60 min	2–3	8–10
Intermediate acting			
NPH	2–4 h	4–10	12–18
Long acting			
Glargine (Lantus®, Sanofi–Aventis)	2–4 h	None	20–24
Detemir (Levemir®, Novo–Nordisk)	2–4 h	3–9	6–24*

*Duration of action is dose dependent.
- Humalog®, Eli Lilly and Company World Headquarters, Lilly Corporate Center, Indianapolis, Indiana 46285.
- NovoLog®, Levemir®, Novo Nordisk, Corporate Headquarters, Novo Allé, 2880 Bagsvaerd, Denmark.
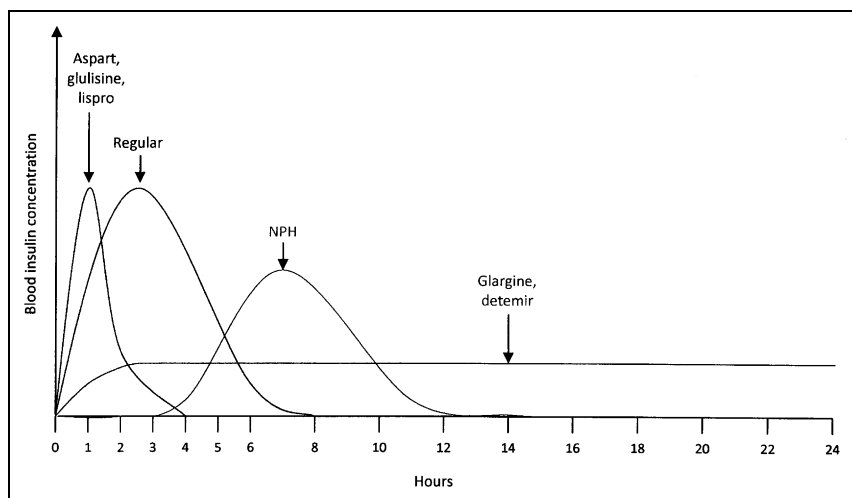- Apidra®, Lantus®, Sanofi-Aventis, 54 rue La Boétie, 75008 Paris, France.

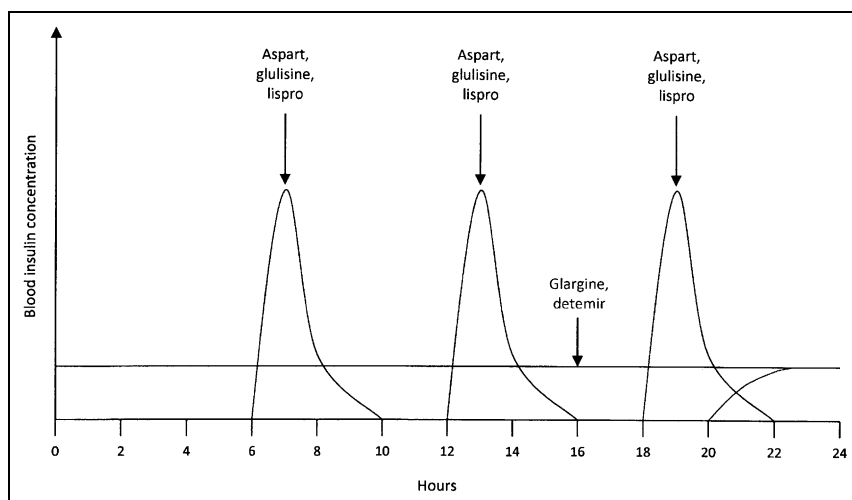Figure 1. Pharmacodynamic profiles of insulin analogs.

Figure 2. Sample "basal–bolus" regimen, with breakfast, lunch, and dinner.

Table 3. Grades of Diabetic Ketoacidosis Severity

	Mild	Moderate	Severe
Venous pH	7.21–7.30	7.11–7.20	<7.10
Bicarbonate (mmol/L)	11–15	6–10	<5

should be considered. For instance, starvation ketosis and alcoholic ketoacidosis can present with ketoacidosis and elevated blood glucose concentrations but rarely are associated with a blood glucose greater than 250 mg/dL. DKA also should be distinguished from other causes of increased anion gap metabolic acidosis, including lactic acidosis, ingestions (eg, methanol, ethylene glycol, salicylates), and renal failure.

After the initial assessment, the key elements of early treatment include frequent monitoring of clinical and biochemical parameters, fluid and electrolyte replacement, correction of hyperglycemia and ketoacidosis, and if necessary, treatment of cerebral edema. During the initial phase of treatment, the patient's heart rate, respiratory rate, blood pressure, neurologic status, capillary glucose level, and fluid output and input status should be assessed hourly. In cases of severe DKA, electrocardiographic monitoring is useful to monitor for evidence of hyperkalemia (eg, peaked T wave, reduced P wave, and widening of QRS complex as severity worsens) or hypokalemia (eg, flattened or inverted T wave, ST segment depression, the presence of a U wave, and a widened PR interval), both of which can lead to cardiac arrhythmia. Checking levels of serum electrolytes, glucose, and blood gasses every 2 to 4 hours is needed to assess response to treatment and to guide adjustments in therapy.

Cerebral Edema

Once the diagnosis of DKA is established, the patient should be assessed for comorbidities associated with DKA. Most critically, the medical team should monitor for signs and symptoms of cerebral edema before and during treatment for DKA. Although rare (occurring in 0.5% to 1% of pediatric cases of DKA), (10) cerebral edema has been associated with a mortality rate of 21% to 24% and permanent neurologic impairment in an additional 15% to 32% of cases. (10) In most cases, cerebral edema occurs 4 to 12 hours *after the initiation of treatment for DKA* (10,11) but can sometimes occur before treatment has been initiated. (8)

Muir and colleagues proposed a bedside, evidenced-based protocol for the early detection of patients at risk for cerebral edema, outlined in Table 4. (11) The authors found that bedside findings of either two major criteria or one major criterion with two minor criteria could identify cerebral edema sufficiently early for intervention. Diagnostic criteria are listed in Table 4 also, but once these signs are present, advanced cerebral edema with the likelihood of significant neurologic injury is also present.

It is important to note that cerebral edema is a clinical, not radiologic, diagnosis because a substantial number of patients with cerebral edema and impending neurologic collapse will have no positive findings on computed tomography of the brain. (11) Thus, imaging studies may be warranted to rule out other causes of neurologic deterioration—although never needed to confirm cerebral edema—but treatment for cerebral edema should not be delayed for confirmatory neuroimaging.

If clinical evidence suggests the presence of cerebral edema, prompt treatment is needed. Early treatment with mannitol (0.25 to 1.0 g/kg) or hypertonic (3%) saline over 30 minutes (5 to 10 mL/kg) may prevent long-term neurologic consequences or death.

Fluid and Electrolyte Therapy

Once intravenous (IV) access is obtained, water and electrolyte deficits need to be replaced in order to restore the circulating volume and the glomerular filtration rate and improve renal clearance of glucose and ketones from the blood. To replace these deficits, most experts recommend using isotonic saline initially and caution against rehydrating the patient too aggressively, suggesting that rehydrating too rapidly using hypotonic solution for initial volume expansion is associated with increased risk for cerebral edema. (7,8) In general, in children with moderate to severe DKA, initial rehydration with 10 to 20 mL/kg isotonic solution (either 0.9% saline or Ringer lactate) over 1 to 2 hours is recommended.

Following the initial fluid resuscitation, the rate of IV fluid should be calculated to run at a rate designed to rehydrate evenly over the next 48 hours. This goal usually can be achieved by running fluids at a rate of 1.5 to 2 times the calculated maintenance rate. Because large amounts of replacement with 0.9% saline has been associated with hyperchloremic metabolic acidosis, (7,8) the IV fluids can be changed to a solution with 0.45% or greater saline with added potassium after at least 4 to 6 hours of fluid replacement with isotonic solution. As insulin is being replaced, an intracellular shift of potassium that leads to a drop in potassium level is seen. For this reason, frequent monitoring is needed as the potassium is replaced and IV fluids are administered.

Insulin

As the fluid and electrolyte deficit is corrected, insulin replacement is needed to normalize the elevated blood glucose and suppress ketogenesis and lipolysis. After the initial 1 to 2 hours of fluid rehydration, continuous IV insulin infusion is started at a rate of 0.1 unit/kg per hour. An initial IV insulin bolus is contraindicated and will cause a rapid drop in blood glucose that may precipitate cerebral edema; in addition, IV insulin's half-life is approximately 7 minutes and therefore cannot suppress ketosis. (7) Ideally, the continuous insulin infusion should lead to a drop in blood glucose at a rate of 50 to 100 mg/dL per hr. In most cases,

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Table 4. Bedside Evaluation of Neurologic State of Children with Diabetic Ketoacidosis

Diagnostic Criteria for Cerebral Edema
- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (eg, grunting, tachypnea, Cheyne-Stokes respirations, apneusis)

Major Criteria
- Altered mentation or fluctuating level of consciousness
- Sustained heart rate deceleration
- Age-inappropriate incontinence

Minor criteria
- Vomiting
- Headache
- Lethargy or not being aroused from sleep
- Diastolic pressure >90 mmHg
- Age < 5 years

Data from Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. *Diabetes Care.* 2004;27 (7):1541-1546. (11)
- The presence of any of the first four diagnostic criteria in the table indicates that advanced cerebral edema is present with the likelihood of significant neurologic injury. Prompt intervention is indicated to limit neurologic injury.
- The presence of two major criteria or one major criterion and two minor criteria represent the presence of early cerebral edema; prompt intervention is indicated to prevent long-standing neurologic injury.
- Signs that occur before treatment should not be considered in the diagnosis of cerebral edema (eg, vomiting before initial treatment should not be counted).

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the hyperglycemia normalizes before the correction of ketoacidosis.

In order to continue infusing insulin to clear the ketoacidosis without inducing hypoglycemia, dextrose can be added to the IV fluids. Many protocols will begin using IV fluids containing 5% dextrose when the blood glucose level drops below 300 mg/dL, then 10% dextrose when blood glucose is less than 200 mg/dL. As insulin continues to be infused and the fluid deficit is replaced, ketoacidosis will resolve. (10) No other intervention besides insulin and IV fluids is indicated to treat the acidosis; bicarbonate should not be used because its use has been associated with cerebral edema. The continuous insulin infusion should be maintained until the ketoacidosis has resolved (ie, pH greater than 7.30 or bicarbonate greater than 17 mmol/L) and the patient is well enough to tolerate oral intake. At this point, IV insulin can be transitioned to a subcutaneous insulin regimen, as described for the patient who initially presents without DKA.

Ongoing Management

Once the medical problems related to the initial presentation have resolved, care shifts towards ongoing management. T1DM is a chronic condition that requires frequent monitoring of blood glucose, frequent dose calculations of numerous injections of insulin analogues with different pharmacokinetic properties, and continual adjustment for alterations in homeostasis, such as stress. Once diagnosed, the initial adjustments in a patient's daily regimen required to achieve effective self-management can seem dramatic and overwhelming.

Yet, in spite of this need for adjustment, the individuals who have T1DM have distinguished themselves in diverse fields. Such individuals include a Supreme Court justice, Olympic gold medalists, internationally recognized scientists, and famous musicians and artists. Their success proves that despite the challenges of T1DM self-management, patients can flourish in the pursuit of their ambitions; however, effective ongoing diabetes education and care is essential for realizing these goals.

Education

After teaching the essential skills of self-management, education transitions towards an ongoing phase seeking to integrate effective diabetes self-management into a daily routine. The patient and family should learn how to handle common contingencies that will affect self-care, such as exercising, dealing with sick days, and traveling. The care team should help facilitate a gradual shift in responsibility for self-care from the parents to the maturing child.

Blood Glucose Monitoring

In order to approach near-normalization of blood glucose concentration, frequent blood glucose monitoring is needed to minimize glycemic excursions and to evaluate the effectiveness of an insulin regimen. More frequent blood glucose monitoring is associated with better glycemic control, and for this reason, four or more tests per day are recommended. (12) Patients and their families should be encouraged to log their blood glucose data, not only to help the diabetes team adjust the insulin regimen but also to gain insight into patterns associated with their own diabetes regimen. The blood glucose log and the glycated hemoglobin (HbA1c) level are useful in quantifying glycemic control and directing titration of insulin doses.

Because glucose becomes irreversibly attached to hemoglobin at a rate proportional to blood glucose concentration, and because the average life span of a red blood cell is roughly 3 months, a measurement of HbA1c correlates well with the average glucose level over the preceding 3 months. In some cases, a fructosamine level is useful because it reflects an average glucose level over a shorter period of 2 to 3 weeks. This test is helpful when patients have a concurrent condition in which hemoglobin turnover is higher, such as hemoglobinopathies or hemolytic anemia, or in situations in which a physician desires an earlier objective assessment of a recent change in therapy.

Insulin Pump

The insulin pump has increased in popularity as an insulin delivery tool over the past two decades. The essential components of most insulin pumps consist of the pump itself, a disposable insulin reservoir, and a disposable infusion set (including a cannula and tubing that connects the cannula to the pump and reservoir). In a manner similar to the basal–bolus regimen, continuous subcutaneous insulin infusion via an insulin pump attempts to mimic the action of the pancreatic β-cell by delivering rapid-acting insulin with basal and bolus components.

Most current-generation pumps allow the user to enter in the number of grams of carbohydrates being eaten and the current blood glucose level and then calculate an appropriate bolus dose according to the patient's I:C ratio and correction factor. The pump can also factor in a mathematical estimate of the amount of active insulin in the circulation at the time of the bolus. Instead of using long-acting insulin analogues, the pump delivers basal insulin by slowly infusing frequent, small aliquots of rapid-acting insulin on a continual basis, effectively giving basal insulin as a continuous infusion.

This approach to basal insulin delivery is a key advantage of the insulin pump over multiple daily injections in that it allows different basal rates at various times of day, which can be used to tailor an insulin regimen to fit variations in insulin sensitivity through a daily cycle. For example, many patients experience an overnight "dawn phenomenon" when circadian rises in growth hormone and cortisol have a glucose-raising effect. To balance this physiologic effect, the overnight insulin basal rate can be titrated up without increasing the daytime basal rate.

Nutrition

Medical nutrition therapy is an important aspect of achieving optimal glucose control. A meal plan should seek to meet the nutritional requirements needed for normal growth and development and fit within the family's routine of meal and snack times, exercise, and cultural norms. Although the nutritional needs are the same for children who have diabetes as for children who do not, intensive insulin therapy to achieve tight glycemic control relies on an accurate assessment of the total amount of carbohydrates being consumed. For these reasons, a medical nutritionist's guidance is needed to help establish a meal plan that meets these needs and to teach families how to measure the carbohydrates in meals and snacks accurately.

A common lay misconception of medical nutrition therapy in T1DM is that calories should be restricted or that certain foods are "off-limits." In general, these principles are influenced by greater familiarity with lifestyle interventions needed in T2DM. Additionally, earlier approaches to insulin therapy relied on fixed doses of mixed insulins and required rigid mealtimes and carbohydrate amounts.

The overall guiding principal for medical nutrition in T1DM today is that the same healthy diet that would be ideal for an individual without diabetes would be ideal for an individual with T1DM. Thus, an appropriate diet seeks to obtain approximately 50% of calories from carbohydrates, 30% from protein, and 20% from fat while limiting saturated fat and cholesterol intake. The medical team should monitor weight gain, keeping in mind that the same factors influencing the rising obesity epidemic also affect patients with T1DM, and that long-term morbidity and mortality associated with obesity can be compounded by the macrovascular and microvascular complications of poorly controlled T1DM. For this reason, any trend toward becoming overweight and obese should be addressed without delay.

Hypoglycemia

Hypoglycemia, biochemically defined as a plasma glucose level of 70 mg/dL or less, is a serious and common drawback to insulin regimens that seek to control blood glucose tightly. On average, hypoglycemia occurs twice weekly in patients intensively treated for T1DM; and severe hypoglycemia, defined as an event in which a patient requires the assistance of another person to administer carbohydrate or glucagon, has an incidence of 1.1 to 1.5 episodes per patient-year. (13,14) Initial symptoms of hypoglycemia include tremor, pallor, weakness, sweating, anxiety, hunger, tachycardia, and transient cognitive impairment. Severe hypoglycemia is associated with significant morbidity and mortality, including cardiac dysrhythmias, seizures, focal neurologic abnormalities, and rarely, permanent neurologic impairment and death.

Diabetes education should teach the patient and family to recognize the symptoms of early hypoglycemia, to check the blood glucose level, and to administer 15 g of rapidly absorbable glucose (eg, glucose tablets) when the blood glucose level is less than 70 mg/dL. The blood glucose should then be rechecked 15 minutes later, with the goal of a glucose level rise to 100 mg/dL or greater. If the glucose level does not rise to 100 mg/dL or greater, another 15 g should be given and the process repeated until the concentration rises to at least 100 mg/dL. Families also should be taught to inject 0.5 to 1.0 mg of glucagon intramuscularly in situations in which the patient has lost consciousness or is otherwise unable to take oral glucose.

Exercise

Exercise positively affects the overall physical, mental, and social health in youth with T1DM. The ability to enjoy physical activity and to develop social skills and confidence through sports participation helps to form a framework for future health as an adult. Exercise presents a challenge to many patients with T1DM, however, because of its propensity to induce hypoglycemia both during and after exercise as glucose utilization and insulin sensitivity increase.

For this reason, patients should be counseled to check blood glucose levels before, during, and after exercise. Before the start of exercise, blood glucose levels should be greater than 100 to 120 mg/dL to decrease the likelihood of exercise-induced hypoglycemia, although, as with all aspects of diabetes, this target should be adjusted empirically based on self-monitoring. During exercise, the glucose level should be checked each hour to target a stable glucose concentration. Families should be counseled that the hypoglycemic effect of exercise can be delayed (eg, occurring overnight after daytime exercise), a process thought to be related to repletion of muscle glycogen stores.

Rather than increasing glucose consumption prior to exercise to prevent hypoglycemia, a preferable approach is to decrease the insulin doses that could affect glycemic levels during exercise. This approach requires consideration of several variables, such as the intensity and duration of exercise as well as the amount of insulin on board. These factors tend to make planning for exercise a process of trial and error.

Sick Day Management

Because the body's stress response to acute illness tends to trigger stress hormones that increase glucose, children with T1DM who experience acute illness should be monitored closely by checking blood glucose and urine ketone concentrations to prevent progression into worsening dehydration and DKA. Although many algorithms for home treatment during illness have been derived, the basic tenants of "sick day" management are that blood glucose and urine ketones should be checked frequently (eg, every 3-4 hours), that insulin should not be withheld even when oral intake is limited, and that supplemental doses of rapid-acting insulin should be given to correct hyperglycemia and suppress ketogenesis (eg, every 3-4 hours). Also, dehydration and subsequent acceleration towards DKA should be prevented by frequent, small sips of fluids.

By carrying out the steps of diabetes sick day management early in the course of an illness, patients who often are in mild to moderate DKA can reverse and resolve acidosis. One algorithm of diabetes sick day rules is presented in Table 5. Patients using insulin pumps should deliver the first dose of rapid-acting insulin with a syringe subcutaneously instead of using the pump to ensure that the insulin is delivered. In most cases, the pump's infusion set should be replaced with a new infusion set to ensure insulin delivery is not being hindered by a "crimp," injection site lipohypertrophy, or other abnormality with the pump or infusion site. Families should be instructed about factors that indicate worsening DKA or impending cerebral edema, such as those listed in Table 4, that would warrant prompt evaluation by a medical team. A postcard with diabetes sick day management steps for patients can be found at http://www.childrenshospital.vanderbilt.org/uploads/documents/vdc_flu_postcard.pdf.

Psychosocial Issues

The diagnosis of T1DM presents a significant stressor to the patient and family as they deal with making significant adjustments to their daily lives to manage the condition. During this time of initial adaptation, many children struggle to make this adjustment, and those who do struggle tend to have difficulty with depression in the early years of living with diabetes. Adolescents in particular often will go through periods of anxiety, denial, and rejection of their diagnosis.

Children who have T1DM are, in general, more likely to suffer from psychological disorders, particularly depression and anxiety, than their unaffected peers. Patients who have psychological disorders are much more likely to have poor glycemic control and hospitalizations for DKA than those who do not. Because of the tendency for patients and families to set self-management patterns and habits in the early years of living with diabetes that are difficult to break, early identification of psychiatric illness is important. Family-based behavioral interventions, such as goal setting, self-monitoring, positive reinforcement, behavioral contracts, supportive parental communication, and shared responsibility for diabetes management at an age-appropriate level, have been shown to affect glycemic management positively. It is important to know that the level of both parents' involvement and acceptance of the condition plays a positive role in optimal glucose control.

Associated Autoimmune Conditions

Patients afflicted with T1DM carry an increased risk for the development of other autoimmune conditions. Autoimmune thyroid dysfunction is the most frequently

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Table 5. **Diabetes Sick Day Rules Algorithm**

Management Steps
1. Check blood glucose level every 3-4 hours until feeling well
2. Give a correction factor dose with rapid-acting insulin every 3-4 hours based upon the blood glucose check (even if not eating)
3. Check urine ketone concentrations every 3-4 hours
4. Encourage fluid intake. Ideally give 1 oz. (30 mL) per year of age per hour in small, frequent sips
- If glucose level is ≥200 mg/dL, sugar-free fluids should be given
- If glucose level is < 200 mg/dL, sugar-containing fluids should be included

Factors warranting medical evaluation
1. Persistent vomiting (eg vomiting more than twice after starting sick day rules) with moderate to large urine ketone levels (or blood ketone levels greater than 1.5 mmol/L)
2. Inappropriately rapid breathing
3. Altered mental status
4. Inability to perform sick day rules

acquired autoimmune condition, with a prevalence of approximately 20% in patients with T1DM. (12) The American Diabetes Association (ADA) therefore recommends measuring a thyroid-stimulating hormone (TSH) level after metabolic control has been established to screen for thyroid dysfunction and then every 1 to 2 years despite previously normal TSH levels, and at any time if growth is abnormal or if clinical suspicion exists for thyroid dysfunction.

When both T1DM and thyroid disease are present, the possibility of coexistent adrenal insufficiency should be considered because the constellation of autoimmune adrenalitis, autoimmune thyroiditis, and T1DM is present commonly in autoimmune polyglandular syndrome type 2.

Patients who have T1DM also are at increased risk for celiac disease, with an estimated prevalence of 4.5%, as compared to approximately 1% in the general population. (12) The ADA additionally recommends that soon after diagnosis, patients with T1DM be screened for celiac disease using tissue transglutaminase antibody or endomysial antibody assays, and subsequently if growth failure or gastrointestinal symptoms occur. (12) Many experts periodically rescreen patients who have negative antibody levels initially. If symptoms are persistent but antibody levels are negative, gastroenterology consultation and endoscopic evaluation should be considered because the sensitivities of these screening antibody tests are modest.

Complications

Long-term complications from T1DM result from the toxic effect of chronic hyperglycemia and manifest as both microvascular disease (nephropathy, retinopathy, neuropathy) and macrovascular disease (coronary artery disease, peripheral vascular disease, stroke). The importance of tight glycemic control to mitigate these effects has been confirmed in large prospective studies. (15,16) Although clinical evidence of these vascular complications usually does not become apparent until the adult years, the underlying pathophysiologic process begins near the time of diagnosis. Additionally, modifiable or treatable risk factors that compound the risk for these comorbidities, such as smoking, hypertension, and hyperlipidemia, become apparent during the adolescent years. For these reasons, the pediatric years present a key opportunity for early detection of these processes and for interventions that would prevent or minimize future morbidity.

– NEPHROPATHY. The earliest evidence of diabetic nephropathy is microalbuminuria (defined as an albumin-to-creatinine ratio of 30 to 299 mg/g in a spot urine sample).

(12) If left unchecked, there is a substantial risk of deterioration to gross proteinuria and, ultimately, to end-stage renal disease. The early detection of microalbuminuria, however, presents an opportunity to reverse the trend toward nephropathy with careful glycemic and blood pressure control. For this reason, the ADA recommends annual screening for microalbuminuria once the patient is age 10 years or older and has had diabetes for at least 5 years. (12)

– RETINOPATHY. Poor glycemic control is associated with substantially increased risk for diabetic retinopathy, a process that begins frequently during the pediatric years; improving glycemic control can minimize the progression of retinopathy. Because retinopathy usually is not recognized earlier than 5 to 10 years after diagnosis and after pubertal onset, the ADA recommends that the first ophthalmologic examination should be obtained after the child is age 10 years and has had T1DM for 3 to 5 years, and routinely thereafter. (12)

– NEUROPATHY. Clinically evident diabetic neuropathy is rare in children and adolescents; but as with the other microvascular complications of T1DM, increased risk is associated with poor glycemic control and disease duration. The ADA recommends annual foot examinations beginning at puberty. (12)

– MACROVASCULAR COMPLICATIONS. Atherosclerotic disease is a major complication of poorly controlled T1DM. Although macrovascular complications rarely become apparent before adulthood, studies evaluating carotid intima media thickness, a sensitive marker for coronary and cerebral vascular disease, have shown the intima to have greater thickness in children, adolescents, and young adults who have T1DM than in their age-matched counterparts. Studies evaluating intensive insulin therapy have demonstrated a significant benefit over standard therapy for reducing the risk of excessive carotid intima media thickness, nonfatal myocardial infarction, stroke, and death from cardiovascular disease. These studies also suggested that long-lasting and fundamental vascular changes occur early in the course of suboptimally controlled T1DM, further emphasizing the importance of tight glycemic control in the pediatric years. (17)

Progress

Despite the disease's challenges, patients with T1DM—once a uniformly fatal condition—can lead lives marked by wellness and achievement through the diligence of effective self-management with assistance from members of a diabetes care team. Emerging research continues to broaden our understanding of the pathogenesis of

T1DM and guide future treatment modalities to improve blood glucose control, lower the rate of diabetes-related complications, and reduce the daily burden of living with T1DM. Immunomodulating therapies, novel insulin analogues, and the artificial pancreas are areas of research that seek to prevent, treat, and cure this condition. As emerging research continues to advance treatment of diabetes, the principles of effective self-management championed by Dr. Joslin will continue to form the foundation for living successfully with T1DM.

Summary

- Type 1 diabetes mellitus (T1DM) is a chronic, lifelong disorder of glucose homeostasis characterized by autoimmune destruction of the insulin-producing pancreatic β-cell, leading progressively to insulin deficiency and resultant hyperglycemia.
- New-onset T1DM can present with the classic findings of polyuria, polydipsia, polyphagia, and weight loss; as diabetic ketoacidosis (DKA), with vomiting, abdominal pain, and lethargy in addition to the classic symptoms; or as an incidental finding discovered on urine or blood testing performed for other reasons.
- DKA is a life-threatening acute complication of T1DM that requires close monitoring for comorbidities, especially cerebral edema. Treatment focuses on rehydration and insulin replacement.
- Because T1DM is a chronic illness, the best possible management is achieved when patients and their families attain ownership of their condition as part of a continuing, empowering relationship with their diabetes care team.
- Optimal health and wellness is achieved when blood glucose is controlled tightly. Intensive control significantly decreases the likelihood of developing the microvascular and macrovascular complications of T1DM.

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1. You see a 12–year–old boy with a complaint of frequent urination. His mother is concerned because her father has had type 2 diabetes mellitus for several years. Urinalysis in the office shows the presence of glucose. You suspect that the boy may have type 1 diabetes mellitus because he also has

    A. Acanthosis nigricans.
    B. An elevated body mass index.
    C. Hispanic heritage.
    D. Hypertension.
    E. Weight loss.

2. A 6–year–old girl is admitted for new–onset hyperglycemia (ie, a fasting blood glucose level greater than 250 mg/dL). She has had symptoms for approximately 2 weeks and looks ill. The most appropriate of the following serum levels to measure first is

    A. Autoantibodies.
    B. Electrolytes.
    C. Insulin.
    D. lipids.
    E. Transaminases.

3. You are reviewing dosage and management of insulin with a 9–year–old girl who weighs 35 kg and has had type 1 diabetes mellitus for several years. You calculate her total daily dose of insulin; she states she is receiving 25 units per day. The following statement that is true and relevant to her dosage is that

    A. After diagnosis of type 1 diabetes mellitus, the "honeymoon phase" lasts approximately 24 months.
    B. Approximately 50% of the total daily insulin prescribed is long acting, with the other 50% being short acting.
    C. The "mixed–split" regimen of insulin dosing allows for greater flexibility in diet than the "basal–bolus" regimen.
    D. Prepubertal children tend to require a higher total daily dose of insulin.
    E. The usual total daily dose of insulin is between 2 and 3 units/kg per day.

4. A 3–year–old boy presents to the emergency department in diabetic ketoacidosis (ie, a blood sugar level of 450 mg/dL). You resuscitate him with isotonic solution and admit him to your intensive care unit for monitoring. He is treated with normal saline and insulin at a rate of 0.1 unit/kg per hour. His blood glucose level gradually falls to 180 mg/dL, but ketosis persists, and the serum bicarbonate concentration is 13 mg/dL. At this time, the most appropriate medical management is to

    A. Add bicarbonate to IV fluids, continue insulin infusion.
    B. Add bicarbonate to IV fluids, discontinue insulin infusion.
    C. Add dextrose to IV fluids, continue insulin infusion.
    D. Add dextrose to IV fluids, discontinue insulin infusion.
    E. Discontinue IV fluids, change to subcutaneous insulin.

5. A 5–year–old girl is undergoing treatment for diabetic ketoacidosis. Her level of consciousness fluctuates, she is vomiting repeatedly, and her diastolic blood pressure is 105 mm Hg. You should immediately

    A. Add bicarbonate to the intravenous fluids.
    B. Administer mannitol.
    C. Administer potassium.
    D. Infuse hypotonic saline solution.
    E. Obtain neuroimaging to look for cerebral edema.

Type 1 Diabetes Mellitus
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