Type 1 Diabetes Mellitus

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

1. Describe the pathogenesis of type 1 diabetes.
2. Review intensive diabetes management protocols, new insulin preparations, and insulin delivery systems.
3. Describe the importance of home glucose and ketone monitoring and the new monitoring methodologies.
4. Elucidate the key elements of the outpatient diabetes examination and screening for diabetes complications.
5. Characterize the importance of the multidisciplinary team in the management and education of children who have type 1 diabetes and their families.

Introduction

Many advances have been made since the Diabetes Control and Complications Trial (DCCT) provided irrefutable evidence of the benefits of following a system of diabetes management that allows for optimal glycemia for patients who have type 1 diabetes. These advances include an ever-increasing armamentarium of types of insulin that have varying onsets and durations of action, insulin delivery systems, improved methods for monitoring glycemia at home, and potential agents that could be used for diabetes prevention or to preserve residual beta-cell function at the time of diagnosis. These exciting advances have enabled the development of comprehensive, intensive diabetes regimens. To increase the success rate for patients and families with these regimens, it is imperative for the multidisciplinary diabetes team and the primary care clinician to work together to support and educate all those who help manage or affect patients.

The pathogenesis of diabetes is reviewed in this article, emphasizing the nearness of expanding efforts at primary prevention and beta-cell preservation at the time of diabetes diagnosis. This is followed by an explanation of current and evolving diabetes management protocols, focusing on insulin regimens and delivery systems that can be used for children to improve glycemic control while minimizing hypoglycemia. Finally, the components of the outpatient visit are reviewed to elucidate methods of screening for diabetes complications to allow early intervention that provides patients with the optimal opportunity to avoid or lessen the devastating microcirculatory and macrovascular complications of the disease.

Pathogenesis

The natural history of type 1 diabetes is shown in the Figure. Beta-cell mass is destroyed gradually over time in genetically susceptible individuals after exposure to environmental triggers that induce T-cell-mediated beta-cell injury and the production of humoral autoantibodies. The degree of beta-cell destruction can be determined by the first-phase insulin response during intravenous glucose tolerance testing. Those who have lost first-phase insulin release are at high risk to develop clinical diabetes. At the clinical onset of disease, a residual beta-cell population still survives that allows for the remission or "honeymoon" period after diabetes is diagnosed. If these cells could be preserved, diabetes management would become significantly less difficult over time. Preserving residual beta-cells, as well as stopping the initial autoimmune beta-cell injury, has become a focus of research interest.

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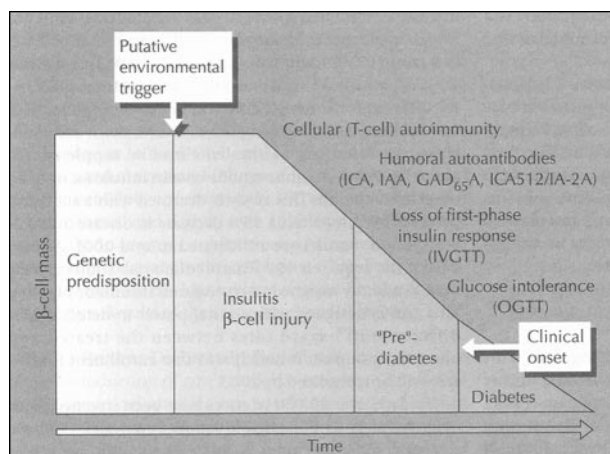
Figure. The natural history of type 1 diabetes. From Morales AE, She JX, Schatz DA. Prediction and prevention of type 1 diabetes. *Curr Diabetes Rep.* 2001;1:28–32. Reprinted with permission from Current Sciences, Inc.

Multiple genetic loci in the major histocompatability (HLA) region predispose to the development of type 1 diabetes. The greatest diabetes susceptibility is conferred by the class II DR and DQ alleles: DR 3/4, DQ 0201/0302, DR 4/4, and DQ 0300/0302. Diabetes risk can be determined by HLA typing of DR/DQ alleles in first- and second-degree relatives and the general population. For example, first-degree relatives who have DR 3/4, DQ 0201/0302 have the highest risk of developing disease (1 in 4 to 5) compared with a risk of 1 in 15 in the general population who has the same genotype.

Multiple environmental factors, to which the individual may be exposed at a very early age, trigger the immune system to destroy the beta-cell mass. The environmental triggers include infectious agents such as viruses, components of the diet, and toxins. Enteroviruses, such as the coxsackie B virus and the rubella virus, may induce islet cell destruction through molecular mimicry. Early exposure to cow milk formula may be diabetogenic in those who have a genetic risk. Diabetes risk also may be increased by failing to supplement young infants with vitamin D. Finally, although it has been hypothesized that the increase in the incidence of diabetes may be due to the widespread institution of immunizations at a young age, an expert panel convened by the National Institutes of Health (NIH) in 1998 found no evidence to support such an association.

The presence of islet cell antibodies (ICA), insulin autoantibodies (IAA), antibodies against glutamic acid decarboxylase (GAD/GAD$_{65}$), and the transmembrane tyrosine phosphatase IA-2 or ICA512 are evidence of islet reactivity. ICA was considered the gold standard for determining autoimmunity in the past. However, biochemical assays for GAD and ICA512 have greater reproducibility, are commercially available, and should be used in the clinical arena to determine the presence of beta-cell autorecognition. The presence of any combination of two or more antibodies indicates a high risk for the development of diabetes.

A number of diabetes prevention trials and networks of collaboration currently are evaluating a variety of strategies to prevent diabetes or to preserve beta-cell mass in patients who have new-onset disease. These include: 1) the Diabetes Prevention Trial – type 1 (DPT-1), which now has expanded into TrialNet; 2) the European Nicotinamide Diabetes Intervention Trial (ENDIT); 3) the Trial to Prevent Diabetes in Genetically at-Risk (TRIGR); and 4) the Immune Tolerance Network, which will study different autoimmune diseases and collaborate with TrialNet.

Conducted in the United States and Canada, DPT-1 evaluated the use of insulin as a diabetes preventive. Administration of parenteral (high-risk cohort) and oral (moderate-risk cohort) insulin was studied in first- and second-degree relatives of people who had diabetes whose risk was determined by the presence of ICA and loss of first-phase insulin release (high-risk cohort) or preservation of first-phase insulin release (moderate-risk cohort). In June 2001, the high-risk arm of DPT-1 was concluded and in June 2003 the moderate-risk arm of DPT-1 ended due to failure to delay or prevent diabetes. In mid-2001, DPT-1 was expanded to become TrialNet. This large multicenter trial supported by the NIH will study other preventives for diabetes and attempts to preserve the limited beta-cell mass present at diagnosis. Agents under potential consideration include antigen-based therapies such as GAD, heat-shock protein, and insulin peptides; monoclonal antibodies such as anti-CD3 and anti-CD25; and immunoregulatory agents such as sirolimus, mycophenolate, intravenous immune globulin, and omega-3 fatty acids.

In Europe, nicotinamide has been assessed in ENDIT because the agent can alter nitric oxide levels and mitigate against beta-cell destruction. It was administered daily in ICA-positive relatives and found not to help delay the onset of diabetes. TRIGR, conducted in Finland, was designed to determine if avoiding cow milk protein for at least the first 6 months after birth can reduce the incidence of diabetes in newborn first-degree relatives. Preliminary data document a reduction in ICA-positivity among those given human milk or protein hydrolysate compared with cow milk formula. If any of

Table 1. The Treatment of Diabetic Ketoacidosis

Initial Approach

- Obtain and monitor vital signs, including blood pressure
- Perform a bedside glucose determination to determine glucose level, then monitor at 30- to 60-min intervals
- Assess the degree of hydration and mental status
- Obtain a urine sample for glucose and acetone; continue to monitor every void
- Draw blood for electrolytes, blood urea nitrogen, venous pH, and complete blood count
- Start an intravenous line and infuse 10 mL/kg of normal saline over 30 to 60 min
- Do not use bolus bicarbonate therapy
- Consult with a pediatric endocrinologist or a pediatric critical care center as soon as possible

Maintenance Therapy

- Administer 0.9% normal saline or 0.66% to 0.45% saline for maintenance plus replacement fluids (correct deficit over 36 to 48 h) at a rate 1½ to 2 times maintenance fluid requirements
- Begin an insulin drip of regular insulin at 0.1 units/kg per hour within 2 h of fluid resuscitation
- Add potassium chloride at 3 to 5 mEq/kg per 24 hours to intravenous fluids; potassium phosphate is not standard but may be used for half of potassium dose
- Follow laboratory parameters, electrolytes and pH every 2 to 4 h initially, then every 4 to 6 h
- Add dextrose to the intravenous fluids: 5% glucose when blood glucose level is 250 to 300 mg/dL (13.9 to 16.7 mmol/L); 10% glucose when blood glucose level is 180 to 200 mg/dL (10 to 11.1 mmol/L). Target decrease in blood glucose level is 80 to 100 mg/dL (4.4 to 5.6 mmol/L) per hour

Calculation of Maintenance Fluids per 24 hours

- 100 mL/kg for the first 10 kg of body weight
- 50 mL/kg for the next 10 kg of body weight
- 20 mL/kg for each additional kg of body weight
  For example: A 25-kg child would receive: For maintenance, 1,000 mL + 500 mL + 100 mL for a total of 1,600 mL/ 24 h or 67 mL/h. For plus replacement if 10% dehydrated, 2,500 mL with ½ given over the first 24 h.

Modified from Kaufman FR, Halvorson M. The treatment and prevention of diabetic ketoacidosis in children and adolescents with type 1 diabetes mellitus. *Pediatr Ann.* 1999;28:576–582.

these or other strategies proves beneficial in delaying the onset of clinical diabetes or in preserving the residual beta-cell mass in patients who have new-onset disease, mass screening of the population to determine those at risk of developing diabetes and treatment of all who have new-onset disease with one or more agents could become standard practice.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) occurs in 25% to 40% of patients who have new-onset disease and in those who have known type 1 diabetes at a rate of 8 per 100 person-years, according to Rewers and associates. In new-onset patients, DKA should be suspected when there is vomiting, dehydration, shortness of breath, abdominal pain, or alteration of the level of consciousness. During the medical evaluation, the clinician should determine any antecedent history of polyuria, polydipsia, weight loss, change in appetite, or decrease in activity, symptoms that suggest diabetes. DKA often is misdiag-

nosed as the "flu" in patients who have known diabetes. Any patient who has diabetes and has been vomiting should be assumed to have DKA until proven otherwise, even if vomiting was precipitated initially by an intercurrent illness. The treatment of DKA, which usually begins in the emergency department, is outlined in Table 1.

DKA remains a major source of morbidity and mortality due primarily to the development of cerebral edema, the gravest complication of DKA. Cerebral edema occurs in 1% to 5% of DKA episodes and is associated with high rates of morbidity and mortality. The onset of cerebral edema is usually within 6 to 12 hours after the initiation of treatment. The warning signs and risk factors are listed in Table 2. In addition, is imperative to monitor vigilantly the patient in whom DKA occurs to detect and treat complications early.

Insulin Preparations

Five categories of available human insulin preparations are available (Table 3). The insulin preparations are

Table 2. Warning Signs and Risk Factors for Cerebral Edema

Warning Signs	Risk Factors
• Headache	• Low initial P_{CO_2}
• Lethargy	• High initial serum urea nitrogen
• Incontinence	
• Seizures	• Lesser increase in serum sodium with therapy
• Pupillary changes	
• Decreasing heart rate	• Treatment with bicarbonate
• Increasing blood pressure	

categorized by the time course of action; those that have a longer onset of action and time to peak action have a longer duration of action. Both rapid-acting and basal insulin have been bioengineered, which confers many advantages.

Manipulation of the insulin molecule through genetic engineering to prevent autoaggregate and maintain its monomeric state allows for a more rapid onset of action and a shorter duration of action among rapid-acting insulin preparations compared with short-acting regular insulin. Insulin lispro (Lys(B28), Pro(B29)) is prepared by switching the amino acid sequence at positions 28 and 29 of the B-chain. Insulin aspart is an analog of human insulin in which the amino acid proline is replaced by aspartic acid at the B28 position. Rapid-acting insulin can be administered immediately after a meal, which is particularly useful in young children in whom food intake may not be reliable. Rapid-acting insulin has been shown to lead to less hyperglycemia after eating and less hypoglycemia in the late postprandial period and at night, although there has been only a minimal decrease or no change in glycosylated hemoglobin (HbA1c) levels with its use in most clinical trials.

Insulin glargine was developed as a basal insulin preparation because it is essentially "peakless." It has two molecules of arginine added to the B-chain, and the A-chain asparagine is substituted with glycine at position 21. This results in a shift of the isoelectric point that allows an onset of action at 1 hour and a duration of action of 24 hours. Insulin glargine cannot be mixed with other insulin preparations. It also has been shown to result in less hypoglycemia in adults. At present, its primary use is as the basal component of multiple-dose insulin regimens (MDI).

Premixed insulin has a fixed ratio of short- or rapid-acting insulin to intermediate-acting insulin. Used in pen injector devices, premixed insulin is available in a number of combinations, such as 70/30 (70% NPH/30% regular), 50:50 (50% NPH/50% regular), and 75/25 (75% NPL [neutral protamine lispro]/25% insulin lispro). Because the ratio of insulin cannot be altered, the role of premixed insulin in pediatrics appears to be minimal.

Inhaled insulin (Exubera®, Pfizer, Groton, CT) has been tested recently in wide-scale clinical trials. Inhaled fast-acting insulin has a peak action at 0.25 to 0.5 hours and a duration of action of 3 hours, similar to that of short-acting regular insulin. Inhaled insulin has been shown in preliminary studies to be effective for the meal bolus in combination with basal insulin by injection. Children as young as 6 years of age have been enrolled in clinical trials, and to date there has been good efficacy and little toxicity, although questions have been raised as to whether there are pulmonary effects. Higher titers of insulin antibodies have been recognized in those receiving inhaled insulin, but the significance of this finding is not known.

A number of devices can be used to administer insulin (Table 4).

Initiation of Insulin Therapy

Although many pediatric patients are hospitalized at the time of diabetes diagnosis, the trend over the

Table 3. The Onset of Action, Peak Action, and Duration of Action of the Five Types of Insulin

Insulin Preparation	Onset of Action (h)	Peak Action (h)	Duration of Action (h)	Maximal Duration (h)
Rapid-acting				
Lispro	1/4 to 1/2	1 to 2	3 to 5	4 to 6
Aspart	1/4 to 1/2	1 to 2	3 to 6	5 to 8
Short-acting				
Regular	1/2 to 1	2 to 4	3 to 6	6 to 8
Intermediate-acting				
NPH (Isophane)	2 to 4	8 to 10	10 to 18	14 to 20
Lente (Zinc suspension)	2 to 4	8 to 12	12 to 20	14 to 22
Long-acting				
Ultralente (Extended zinc suspension)	6 to 10	10 to 16	18 to 20	20 to 24
Basal				
Glargine	1 to 2	None	19 to 24	24

Table 4. Insulin Injection Devices
• **Insulin Syringes**
— Regular or short needles
— 0.3, 0.5, 1.0 cc
• **Indwelling Catheters**
• **Pen Devices**
— Disposable
— 1- or 0.5-unit increments
— Combined with glucose meter
• **Automatic Injection Devices**
• **Jet Injectors**
• **Insulin Pumps**
— Four manufacturers

Table 5. Blood Glucose and Ketone Monitoring
• ***Before breakfast***
• ***Before lunch***
• ***Before dinner***
• ***Bedtime***
• Nighttime: Midnight, 0300
• Postprandial: 2 h
• Presnack
• After school
• Intermittent: Mid-morning, during illness, pre- or postexercise, during travel or changes in routine
• Ketone—blood or urine: sustained hyperglycemia, during illness, with CSII
Times in bold and italicized are the routine and minimal times for blood glucose monitoring.

last decade has been to initiate outpatient insulin therapy for those who are not acidotic or dehydrated at diagnosis. These patients and those who have recovered from DKA are started on three insulin injections per day, although some may be placed on two injections. Those receiving three injections are given 2/3 of the total dose in the morning (1/3 rapid or short-acting, 2/3 intermediate-acting), 1/6 of the total at dinner as rapid or short-acting insulin, and 1/6 of the total before bed as intermediate-acting insulin. The initial total amount of insulin varies. For children recovering from DKA, up to 1 to 2 U/kg per day of insulin may be required. Younger children and those who are not ill at presentation may be treated with 0.5 to 1 U/kg per day.

Within 1 month of diagnosis, most pediatric patients who have type 1 diabetes enter a remission or "honeymoon" phase, although this may not occur in very young children. Patients require little exogenous insulin during this phase, often less than 1/3 U/kg per day, but they should not be weaned off insulin injections. In the future, as clinical trials attempt to determine if residual beta-cell mass can be preserved with immunomodulatory therapy to induce tolerance, patients will continue to be maintained on insulin therapy. Therefore, discontinuation of insulin therapy should not be expected or used as an indication of the efficacy of immunomodulatory agents.

Regimens

The basic concept of insulin therapy is to attempt to mimic normal physiology. To do this, two or three insulin injections per day may not be sufficient. As a result, basal-bolus regimens (intensive therapy, flexible therapy) that use multiple injections (four or more) or insulin pump therapy (continuous subcutaneous insulin infusion [CSII]) have been devised that provide sufficient insulin throughout the 24-hour period to cover basal insulin requirements as well as boluses of insulin to match carbohydrate and food intake.

Recently, it has become evident that young children, children, and youth can use basal-bolus regimens that involve multiple injections per day or insulin pumps. Success occurs when the regimens are coupled with education, support, dosage adjustment algorithms, and close monitoring of the blood glucose level.

The basal component of MDI is intermediate-, long-, or basal-acting insulin administered either twice daily before breakfast and bedtime or once every 24 hours (usually before bedtime). Bolus doses are given as either rapid-acting insulin immediately before the meal or short-acting insulin 20 to 30 minutes before the meal. The amount of the bolus dosage is determined by the amount of insulin needed for the carbohydrate content of the meal (and protein content, if indicated) and for the premeal glucose level. Generally, the basal insulin doses account for 50% of the total daily insulin requirement and the bolus doses comprise the other 50%. Insulin pump therapy may be the most effective basal-bolus regimen and the optimal one for children of any age. Insulin pump therapy has been shown to be ideal for patients wishing to optimize glycemia, improve lifestyle, reduce hypoglycemia, and prevent recurrent DKA or progression of complications.

Table 6. Advances in Glucose Monitoring

- Very small blood samples required
- Forearms can be used for preprandial samples
- Results available in 5 to 45 sec
- Glucose meters can fit in a pocket
- Glucose meters store glucose values
- Glucose values can be displayed in a variety of forms and graphs
- Continuous or near continuous glucose monitoring
  - The Medtronic MiniMed® system
    - Uses a glucose oxidase sensor
    - Measures subcutaneous glucose levels every 5 min
    - Is worn for up to 3 d
    - Glucose results analyzed retrospectively
  - The GlucoWatch® system
    - Uses iontophoresis
    - Measures glucose content of interstitial fluid every 20 min
    - Is worn for up to 12 h
    - Contains alarms to detect hyper- and hypoglycemia
    - Gives real-time value
    - Is associated with minor skin irritation in some individuals

Blood Glucose and Ketone Monitoring

All patients who have type 1 diabetes, and particularly those receiving basal-bolus regimens, must monitor blood glucose levels (Table 5). It is critical to measure the blood glucose level several times during the day and intermittently during the night. The frequency of blood glucose monitoring is highly associated with glycemic control. Levine and colleagues described a large cohort of youth, 7 to 16 years of age, in whom frequency of blood glucose monitoring was the sole modifiable predictor of HbA1c levels.

Many advances have made home glucose monitoring easier, faster, less painful, and more relevant (Table 6). In addition, semi-invasive, continuous, or near-continuous glucose monitoring devices have been developed. In the research setting, these glucose monitoring systems, such as the Medtronic MiniMed CGMS® (Medtronic Mini Med, Inc, Northridge, CA) and the Cygnus Gluco-Watch® Automatic Glucose Biographer (Cygnus, Inc, Redwood City, CA) have been shown to facilitate identification of glycemic patterns and trends and lead to improved glycemic control. When continuous systems can be used clinically to provide real-time continuous glucose levels, a marked improvement in short- and long-term diabetes outcome likely will occur. Eventually, these systems may be linked to insulin infusion devices, creating a near-artificial pancreas.

Glycemic Targets

The rate-limiting step in the intensification of diabetes management is the occurrence of severe hypoglycemia. Because young children appear to be more susceptible to severe hypoglycemia, the target range for blood glucose levels and for HbA1c values are generally higher for them (Table 7). However, multiple studies have shown no association between HbA1c levels and severe hypoglycemia and no increase in hypoglycemia among those who have low HbA1c values following intensive diabetes regimens. Recently, Levine and colleagues showed that with an overall hypoglycemia event rate of 62 events per 100 person-years, there was a high incidence of hypoglycemia even among those who had poor metabolic control. Therefore, fear of hypoglycemia generally should not deter patients and families from following intensive regimens and attempting to improve glycemic control.

To adjust insulin dosages to optimize glycemia, multiple algorithms can be used to correct an abnormal glucose level, match carbohydrate intake, and account for exercise and activity (Table 8). Table 9 outlines principles for adjusting the basal or set dosage of insulin.

The Outpatient Visit

Pediatric patients who have diabetes should have comprehensive, multidisciplinary outpatient visits at regular quarterly intervals. The purpose of these visits is to:

- Assess health status
- Adjust the diabetes regimen as indicated
- Promote diabetes knowledge and competency
- Motivate patients and families to improve short- and long-term outcome

During outpatient visits, it is important to obtain a comprehensive

Table 7. HbA1c and Glycemic Targets

	HbA1c (%)	Premeal (mg/dL [mmol/L])	Postmeal (mg/dL [mmol/L])
Infants, Toddlers	<7.5 to 8.5	100 to 180 (5.6 to 10)	<200 (11.1)
School-age children	<8.0	70 or 80 to 150 (3.9 or 4.4 to 8.3)	<200 (11.1)
Teens	<7.5	70 to 140 or 150 (3.9 to 7.7 or 8.3)	<180 (10)

Table 8. Insulin Dosage Adjustment Algorithms

Insulin doses need to be adjusted for the following:

1. **Correct for an abnormal blood glucose level (correction algorithm)**

   ▪ The amount of insulin given per the correction algorithm can be determined by taking into account age or insulin dosage

Insulin Dosage	Age	Amount/50 mg/dL (2.8 mmol/L) That Blood Glucose is Elevated
<5 U	<5 y	0.25 U
5 to 10 U	6 to 9 y	0.50 U
10 to 20 U	10 to 12 y	1 U
>20 U	Teens	1.5 to 2 U

   ▪ The insulin dose also can be determined by insulin sensitivity by using the 1800 or 1500 Rule. The 1800 Rule is used for rapid–acting insulin and the 1500 Rule for short–acting insulin. Insulin sensitivity is determined by dividing 1800 or 1500 by the total daily dose of insulin to determine how many mg/dL (mmol/L) that 1 unit of insulin decreases the glucose level

2. **Account for exercise and activity**

   ▪ Decrease insulin dose, add carbohydrate, or both
   ▪ For activity lasting $1/2$ to 2 hours, a child probably will need to take 10 to 15 g of carbohydrate for every $1/2$ to 1 h
   ▪ Occasionally, activity can elevate blood glucose levels. This usually occurs in the afternoon for children taking 2 or 3 insulin injections per day or if CSII is disconnected for more than 1.5 to 2 h
   ▪ With repeated strenuous physical activity, the total daily insulin dose may need to be decreased by 10% to 20%

3. **Match carbohydrate intake (insulin:carbohydrate ratio or carbohydrate supplement)**

   ▪ Divide 450 by the total units of insulin used per day to determine the number of grams of carbohydrate that requires 1 unit of insulin

4. **Anticipate a change in the usual regimen (anticipatory supplement)**

interval history. As outlined in the American Diabetes Association Clinical Practice Recommendations for 2001, and modified for pediatric patients, the following should be determined:

• Frequency, causes, and severity of hypoglycemia or hyperglycemia
• Results of home glucose monitoring from logbooks and blood glucose meter downloads
• Self-adjustments to the diabetes regimen
• Integration of home care management behavior and understanding of the diabetes management plan and goals
• Assessment of education and needs

• Review of systems for intercurrent problems or diabetes complications
• Current medications
• Psychosocial issues
• Changes in life situations
• School performance and after school, weekend, and sports activities
• Risk-taking behavior, particularly for adolescents

Diabetes clinicians should ensure that the patient has routine pediatric care during health supervision visits to diagnose and treat other medical/psychosocial problems and to administer immunizations and anticipatory guidance.

A comprehensive physical examination with appropriate laboratory monitoring should emphasize areas depicted in Table 10.

Prognosis and Long-term Complications

Prevention of long-term microvascular and macrovascular complications of diabetes must begin during the pediatric age range because there is no "grace" period. Complications appear very early in the course of diabetes, perhaps at the onset of disease, and the earliest stages often can be seen within 2 to 5 years after diagnosis. Because the long-term complications are affected by diabetes duration and glycemic control, appropriate diabetes management aimed at reducing glycemic burden is critical for all affected children and youth. The DCCT showed that intensive diabetes management was associated with the following percent risk reductions:

• Primary retinopathy, 76%
• Progression of retinopathy, 54%
• Development of proliferative or severe nonproliferative retinopathy, 47%
• Microalbuminuria, 39%
• Frank albuminuria, 54%
• Clinical neuropathy, 60%

Table 9. Principles for Adjustments in Basic or Set Insulin Dose

Rapid-, short-, intermediate- or long-acting insulin is adjusted after a pattern has been identified over 3 to 7 days Increase or decrease by 0.5, 1.0, 1.5, or 2.0 U (10% of the dose)	
Time of Abnormal Test	**Change This Insulin**
Two or Three Insulin Injections	
Before breakfast	Evening intermediate- or long-acting
Before lunch	Morning rapid- or short-acting
Before dinner	Morning intermediate- or long-acting
Before bedtime	Evening rapid- or short-acting
In the night	Evening intermediate- or long-acting
Multiple Insulin Injections	
The same as above except:	
Before dinner	Lunch rapid- or short-acting
Insulin Pump	
Change bolus dose if blood glucose abnormal	<2 to 3 h after the meal
Change basal dose if blood glucose abnormal	>3 h after the meal
Recheck to be sure the changes made return blood glucose levels to the target range	

Modified with permission from Kaufman FR, Halvorson M. New trends in managing type 1 diabetes. *Contemp Pediatr.* 1999;16:112–123.

In addition to glycemia, other risk factors for diabetes complications include family history or genetic predisposition, hyperlipidemia, hypertension, smoke exposure, and the pubertal augmentation of hormonal secretion, particularly growth hormone. The association of macrovascular disease and glycemic control has been demonstrated; both a direct effect of hyperglycemia and an indirect effect, perhaps through lipid metabolism, promote arteriosclerosis.

Conclusion

Many advances have been made in diabetes management over the last 1 to 2 decades that involve improved insulin preparations, insulin delivery systems, glucose and ketone monitoring, and laboratory assessment. In addition, there is an expanded understanding of the

Table 10. The Outpatient Visit

Physical Examination	Frequency/Recommendations
Weight, height, body mass index	Every 3 mo/assess changes in percentile
Sexual Maturity Rating Stage	Every 3 mo/note pubertal progression
Blood pressure	Every 3 mo/target <90th percentile for age
Eye	Dilated funduscopic examination every 12 mo after 5 y of diabetes
Thyroid	Every 3 mo/presence of goiter, signs of thyroid dysfunction
Abdomen	Every 3 mo/presence of hepatomegaly, fullness, signs of malabsorption, inflammation
Foot, peripheral pulses	Every 3 mo inspection/after age 12 y, thorough examination for sensation, pulses, vibration yearly
Skin, joints, injection sites	Every 3 mo/injection sites, joint mobility, lesions associated with diabetes
Neurologic	Every 12 mo/signs of autonomic changes, pain, neuropathy
Laboratory Test	**Frequency**
HbA1c	Every 3 mo
Microalbuminuria	Every 12 mo after puberty or after 5 y of diabetes
Urinalysis, creatinine	At presentation and with signs of renal problems
Fasting lipid profile	After stabilization at diagnosis and every few years
Thyroid function tests, including antithyroid antibodies	Every 12 mo
Celiac screen	At time of diagnosis, if symptoms, at puberty
Islet antibodies	At diagnosis

pathogenesis of diabetes and the potential to prevent total beta-cell destruction. Further advances are anticipated over the next years as research progresses toward the cure of this devastating disorder. At present, the importance of effective daily management of diabetes must be emphasized. Follow-up visits must occur to ensure optimal physical and psychosocial outcome. The patient, parents, family members, school and child care personnel, diabetes team, and primary care clinician must work in a partnership committed to a multicomponent diabetes regimen that is as intensive and safe as possible.

Suggested Reading

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. You are evaluating a 13-year-old girl who has a 6-year history of type 1 diabetes. She has a known history of noncompliance with her insulin therapy. She complains of abdominal pain, and she appears mildly dehydrated. A serum glucose level is 650 mg/dL (36.1 mmol/L). Her urinalysis is positive for glucose and ketones, and a venous pH is 7.20. Of the following, the most appropriate *initial* management step is to:

   A. Administer a bolus of 10 to 20 mL/kg normal saline.
   B. Administer an intravenous bicarbonate infusion.
   C. Begin an insulin drip at a rate of 0.5 U/kg per hour.
   D. Obtain a glycosylated hemoglobin level.
   E. Start two times maintenance fluid requirements with ½ normal saline and potassium.

2. Which of the following statements regarding the development of type 1 diabetes is *true*?

   A. Administration of parenteral insulin to those at risk has been proven to decrease the likelihood of developing diabetes.
   B. HLA typing has not been shown to be useful in determining the risk of developing diabetes.
   C. Most patients have complete destruction of the beta cells, with no residual function at the time of diagnosis.
   D. The presence of antibodies against islet cells and insulin can be predictive of the risk of developing diabetes.

3. You are managing a 14-year-old boy who has diabetic ketoacidosis in the pediatric intensive care unit. He had an initial blood glucose level of 560 mg/dL (31.2 mmol/L), and so far he has received a normal saline bolus. Which of the following statements regarding the further management of this patient is *true*?

   A. Bicarbonate should be added to the fluids if signs of cerebral edema develop.
   B. Glucose should be added to the fluids once the blood glucose levels are 100 mg/dL (5.6 mmol/L) or less.
   C. Insulin initially should be administered subcutaneously as a combination of regular and intermediate-acting forms.
   D. Potassium should be added to the intravenous fluids only if the potassium levels decrease below 3.5 mEq/L (3.5 mmol/L).
   E. The blood glucose should decrease by 80 to 100 mg/dL (4.4 to 5.6 mmol/L) per hour.

4. Which of the following statements regarding insulin therapy is *true*?

   A. Inhaled insulin is not effective in children.
   B. Insulin pump therapy should be reserved for noncompliant adolescent patients.
   C. Insulin therapy should be discontinued temporarily during the "honeymoon" period.
   D. Rapid-acting insulin is beneficial because it decreases glycosylated hemoglobin levels over time.
   E. The use of rapid-acting insulin can decrease postprandial hyperglycemia and nighttime hypoglycemia.

5. You are seeing a 9-year-old boy who was diagnosed with type 1 diabetes 2 years ago. He currently receives two daily injections of short- and intermediate-acting insulin. As part of your evaluation, you ask to see his blood glucose diary. You note that most of his morning readings over the last month have been around 200 mg/dL (11.1 mmol/L). His mother is unwilling to try an insulin pump at this point. Which of the following management options is the *best*?

   A. Increase the evening dose of short-acting insulin.
   B. Increase the morning dose of intermediate-acting insulin.
   C. Increase the morning dose of short-acting insulin.
   D. Obtain a HgA1C level, and if it is normal, continue the current insulin regimen.
   E. Split the evening dose to administer intermediate-acting insulin at bedtime.