

PediatricsⁱⁿReview[®]

Type 1 Diabetes Mellitus in Pediatrics

David W. Cooke and Leslie Plotnick

Pediatr. Rev. 2008;29;374-385

DOI: 10.1542/pir.29-11-374

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pedsinreview.aappublications.org/cgi/content/full/29/11/374>

Pediatrics in Review is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1979. Pediatrics in Review is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2008 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0191-9601. Online ISSN: 1526-3347.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



Type 1 Diabetes Mellitus in Pediatrics

David W. Cooke, MD,*

Leslie Plotnick, MD[†]

Author Disclosure
Drs Cooke and Plotnick have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

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

1. Describe the pathogenesis of type 1 diabetes.
2. Identify acute and chronic complications of type 1 diabetes.
3. Discuss management options and treatment goals for type 1 diabetes.

Introduction

Diabetes mellitus is a disorder of the metabolic homeostasis controlled by insulin, resulting in abnormalities of carbohydrate and lipid metabolism. Type 1 diabetes (also called juvenile-onset diabetes mellitus and insulin-dependent diabetes mellitus) is caused by an absolute insulin deficiency, the result of a loss of the insulin-producing beta cells of the pancreas. Type 2 diabetes mellitus is characterized by two underlying defects. The earliest abnormality in an individual who develops type 2 diabetes mellitus is insulin resistance, which initially is compensated for with an increase in insulin secretion. Type 2 diabetes mellitus then develops due to a defect in insulin secretion that prevents such secretion from matching the increased requirements imposed by the insulin-resistant state. Thus, diabetes mellitus always is caused by insulin deficiency: in type 1 diabetes mellitus, the deficiency is absolute; in type 2 diabetes mellitus, the deficiency is relative.

Although the percentage of cases of diabetes in children and adolescents caused by type 2 diabetes has risen in the past 1 to 2 decades, type 1 diabetes remains the most common form of diabetes mellitus in children.

Recombinant insulin analogs, insulin pumps, and newer devices for home monitoring have drastically improved the ability to control glucose concentrations in patients who have diabetes. However, the feedback control in the healthy state that allows minute-to-minute regulation of insulin secretion cannot be recapitulated with current diabetes therapies, making full metabolic normalization not yet possible. Thus, some degree of hyperglycemia persists in virtually all patients who have diabetes. Long-term complications, including renal failure, retinopathy, neuropathy, and cardiovascular disease, are related to and likely caused by the hyperglycemia.

Epidemiology

In the United States, the prevalence of type 1 diabetes at 18 years of age is approximately 2 to 3 per 1,000. Type 1 diabetes typically has its onset in childhood, although it can present at any age from infancy to adulthood. Recent studies have documented an increase in the incidence, both in the United States and in other western countries, with the incidence in the United States approaching 20 cases per 100,000. There are small peaks in incidence at 2 and 4 to 6 years of age and a larger peak at 10 to 14 years of age. The incidence is approximately 1.5 times higher in American nonHispanic white people compared with African American or Hispanic individuals. There is seasonal variation in the incidence of type 1 diabetes, with more cases presenting in the cooler months of the year.

Pathogenesis

Type 1 diabetes is caused by the autoimmune destruction of the beta cells of the pancreas. Autoimmune type 1 diabetes sometimes is referred to as type 1A; type 1B diabetes is a rare

*Associate Professor, Department of Pediatrics, Division of Pediatric Endocrinology, Johns Hopkins University School of Medicine, Baltimore, Md.

[†]Professor, Department of Pediatrics, Division of Pediatric Endocrinology, Johns Hopkins University School of Medicine, Baltimore, Md.

form of insulinopenic diabetes that is found most often in patients of African or Asian ancestry, in whom autoimmunity is not believed to cause the islet cell loss. In this review, “type 1” diabetes refers solely to type 1A diabetes.

Type 1 diabetes is believed to develop when environmental triggers stimulate an autoimmune reaction against pancreatic beta cells in a genetically susceptible individual. The largest genetic component of the risk of diabetes is the major histocompatibility complex on chromosome 6, including the DR3-DQ2 and DR4-DQ8 alleles that increase risk and the DR2-DQ6 allele, which is protective. Because of the genetic component of risk for the disease, the risk for diabetes is increased in relatives of individuals who have diabetes (Table 1). In spite of this familial risk, however, only 10% to 20% of individuals who have type 1 diabetes have a similarly affected family member.

A number of toxins, dietary components, and viral infections have been proposed as possible environmental factors contributing to the pathogenesis of type 1 diabetes. Except for congenital rubella infection, after which up to 20% of affected individuals develop type 1 diabetes, the identity of other specific environmental factors remains either unconfirmed or unidentified.

The autoimmune destruction of pancreatic beta cells is a T-cell-mediated process. In addition, autoantibodies directed against beta-cell antigens usually are identified in the sera of patients who have type 1 diabetes. These substances include antibodies detected against whole

islets (islet cell antibodies) as well as antibodies against specific proteins such as insulin, glutamic acid decarboxylase, and a protein tyrosine phosphatase, insulinoma-associated protein-2. These antibodies can be detected months to years before the development of diabetes. However, such antibodies are not likely to have a direct role in the beta-cell damage.

Indeed, not all individuals who have beta-cell autoantibodies develop diabetes. Nonetheless, the presence of the antibodies indicates an increased risk of developing diabetes, with the presence of multiple such antibodies more predictive of future type 1 diabetes than is a single antibody. The increased risk is much higher in populations having additional risk factors, such as relatives of individuals who have type 1 diabetes or individuals who have high-risk human leukocyte antigen (HLA) haplotypes. Thus, the antibodies have very poor predictive utility as a “screen” in the general population.

The autoimmune destruction of beta cells probably occurs over the course of months to years before diabetes develops. It is believed that more than 80% of beta cells must be lost before glycemic control is impaired significantly. As beta-cell loss progresses beyond that point, insulin is insufficiently present to maintain glucose and lipid homeostasis. When glucose concentrations in the blood rise above approximately 180 mg/dL (10.0 mmol/L), glucosuria occurs, leading to an osmotic diuresis that causes polyuria. The polyuria stimulates polydipsia to maintain euvoemia. With further insulin deficiency, there is an increase in lipolysis from fat cells as well as protein breakdown, an exaggeration of the normal fasting state designed to provide alternative sources of fuel. These mechanisms, along with the caloric loss from glucosuria, result in the hyperphagia and weight loss typical of the undiagnosed diabetic state. With profound insulin deficiency, the process devolves into ketoacidosis, with marked hyperglycemia, dehydration driven by the glucosuric osmotic diuresis, and accumulation of ketoacids from the hepatic metabolism of the liberated fatty acids.

Diagnosis

The diagnosis of type 1 diabetes generally is straightforward, with the child’s presenting symptoms suggesting the diagnosis and laboratory studies confirming its presence. The classic symptoms of diabetes are polydipsia, polyuria, polyphagia, and weight loss. Re-emergence of bedwetting, nocturia, and a need to leave classes in school to use the bathroom are complaints that suggest polyuria. The symptoms of undiagnosed diabetes typically are present for less than 1 month, although they may

Table 1. Risk of Developing Type 1 Diabetes for Individuals Who Have an Affected Relative

Sibling	Risk
Overall	6%
Identical twin	<50%
HLA identical	15%
HLA haploidentical	6%
HLA nonidentical	1%
Offspring	Risk
Overall	5%
Father who has IDDM	6%
Mother who has IDDM	2%

HLA=human leukocyte antigen, IDDM=insulin-dependent diabetes mellitus

be present for several months in some. The other typical presentation for children who have type 1 diabetes is metabolic deterioration into diabetic ketoacidosis (DKA), presenting with nausea, vomiting, dehydration, and lethargy. Affected patients generally have a preceding history of the classic symptoms of diabetes. In both of these situations, a plasma glucose concentration greater than 200 mg/dL (11.1 mmol/L) confirms the diagnosis. A fasting glucose value of 126 mg/dL (7.0 mmol/L) or more also is diagnostic.

It is highly desirable to diagnose type 1 diabetes before the child's metabolic state deteriorates into DKA to avoid the morbidity and mortality risk associated with this condition. Therefore, it is important to be attentive to children who have polydipsia and polyuria or weight loss in spite of polyphagia and to test such children for diabetes. However, although the autoimmune process that leads to beta-cell failure in type 1 diabetes may be present for many years prior to the clinical presentation of diabetes, the period of time from when abnormalities in glucose control can be identified until the development of symptoms generally is relatively brief. Therefore, screening for type 1 diabetes is not useful.

In certain situations, the diagnosis of diabetes should be considered in the absence of the classic symptoms. Examples include an infant who presents with an acute febrile illness in whom a plasma glucose value obtained as part of a chemistry panel is elevated. This scenario may result from hyperglycemia as part of an acute stress response to the illness or it may be the coincident presentation of diabetes with a viral illness. Another example is the situation in which results of a urinalysis (obtained, perhaps, as a routine health maintenance laboratory study) indicates glucosuria in the absence of a history of polydipsia or polyuria. This finding may indicate renal tubular dysfunction but also may be due to diabetes identified in a presymptomatic state.

In the absence of symptoms, the diagnosis is based on a fasting plasma glucose value at or above 126 mg/dL (7.0 mmol/L). Although virtually never needed for the diagnosis of type 1 diabetes, a 2-hour postchallenge plasma glucose value at or above 200 mg/dL (11.1 mmol/L) on an oral glucose tolerance test also is diagnostic. In the absence of unequivocal hyperglycemia, abnormal results of these tests warrant repeated tests on a subsequent day to confirm the diagnosis.

In the past, the diagnosis of diabetes in a child was presumed to be type 1 diabetes. Since the 1990s, however, the incidence of type 2 diabetes in children and adolescents has risen dramatically, driven in large part by the increased prevalence of obesity. Indeed, a recent

population-based study found that one third of new diabetes cases in children 10 to 19 years of age were due to type 2 diabetes. Much of this increase was due to the very high proportion of type 2 diabetes among minority children (African American, Hispanic, Asian/Pacific Islander, Native American), in whom more than 50% had type 2 diabetes. A significant 15% of nonHispanic white children, however, also had type 2 diabetes. Thus, once diabetes is diagnosed, at least some consideration of whether the child has type 1 or type 2 diabetes (or one of the more uncommon forms of diabetes) is necessary because this determination may affect the choice of treatment.

Although some children present with type 2 diabetes before puberty, most prepubertal children develop type 1 diabetes. Similarly, it generally is not necessary to consider the diagnosis of type 2 diabetes in a nonHispanic white child who presents in DKA or who is lean (eg, has a body mass index less than the 85th percentile for age). Conversely, a child who is diagnosed with diabetes because of being screened as an at-risk child is considered to have type 2 diabetes without the need for additional investigation.

However, for obese, nonHispanic white children 10 years of age and older, as well as for most minority children in this age group, the possibility that the diabetes is type 2 rather than type 1 should be considered in those presenting with symptoms. In spite of data indicating that a significant percentage of children or adults who otherwise appear clinically to have type 2 diabetes are found to have beta-cell autoantibodies, the presence of such antibodies in new-onset diabetes is still highly suggestive of type 1 diabetes. Conversely, the absence of multiple beta-cell autoantibodies argues against a diagnosis of type 1 diabetes.

Other, rarer types of diabetes may be considered in specific clinical situations. Maturity-onset diabetes in youth (MODY) could be considered in an adolescent who has a family history consistent with autosomal dominant inheritance of noninsulin-dependent diabetes with onset in the second or third decade of life. Onset of diabetes in infancy raises the possibility of monogenic forms of diabetes due to mutations in the genes encoding the adenosine triphosphate-sensitive potassium channel of the beta-cell (*KCNJ11*, encoding the Kir6.2 subunit, and *ABCC8*, encoding the SUR1 subunit) or a mutation in the insulin gene. A diagnosis of either MODY or neonatal diabetes due to *KCNJ11* or *ABCC8* mutations allows consideration of treatment with oral hypoglycemic agents that stimulate endogenous insulin secretion through binding to the sulfonylurea receptor (SUR1).

Prevention

It is possible to identify individuals at high risk of developing type 1 diabetes through tests for autoantibodies, HLA typing, and other tests. Ongoing studies, such as the Diabetes TrialNet and the Trial to Reduce IDDM in the Genetically at Risk (TRIGR), seek to identify interventions to prevent diabetes in high-risk individuals. Currently, however, no successful prevention has been identified. Outside of such clinical trials, therefore, there is no indication for screening individuals to identify those at risk.

At the time of diagnosis with type 1 diabetes, significant beta-cell function remains, perhaps 10% to 20% of the function present prior to the onset of the immune destruction. Secondary prevention refers to the possibility of interrupting the immune process to preserve residual beta-cell function. The benefit of such prevention is evident when considering the treatment of individuals during the “honeymoon” period, a time when residual function is present. Treatment at this time is much more

“Although uncertain oral intake puts the patient at risk for hypoglycemia from insulin therapy, insulin treatment must be continued to prevent deterioration into DKA.”

successful than is therapy applied after endogenous insulin production has stopped. Although no such treatment of proven benefit has been identified, ongoing studies are investigating such treatments through the Diabetes TrialNet and the Immune Tolerance Network.

Transplantation

Whole or partial pancreas transplantation or transplantation of isolated islets via intraportal infusion can replace the beta cells destroyed by immune destruction in type 1 diabetes. Such transplants require immunosuppression to prevent alloimmune rejection of the graft and to prevent beta-cell destruction from the underlying diabetes immune attack. The risks of transplantation remain too high to consider its use in most patients and specifically in pediatric patients. However, for patients already requiring immunosuppression for a kidney transplant, pancreas transplantation is an appropriate consideration. In addition, current protocols have increased the success and decreased the toxicities of immunosuppression for

islet cell transplants. However, significant toxicities remain. Therefore, islet cell transplantation remains a consideration in only a highly select group of patients, typically adults who have severe hypoglycemic unawareness.

Complications

The goal of treatment in type 1 diabetes is to avoid the acute and chronic complications of the disease. DKA and hypoglycemia are the most significant acute complications of diabetes and its treatment, and both complications pose a significant risk of morbidity and mortality. Diabetes mellitus causes damage to the microvascular circulation, which results in tissue and organ damage, most notably in the retina, kidneys, and nerves. Due to these microvascular complications, diabetes mellitus is a leading cause of blindness, end-stage renal disease, and neuropathy. There also is a significant increase in the risk of atherosclerotic vascular disease in individuals who have diabetes. This macrovascular disease is responsible for strokes and heart attacks being the most common causes of death in these patients.

Decreasing the Risk of Long-term Complications

Both the microvascular and macrovascular complications of diabetes are related to the hyperglycemia that persists even with disease treatment. The development of chronic complications also depends on the duration of diabetes,

generally taking decades for clinically significant complications to appear. Therefore, although some late adolescents who have early onset of diabetes may show early evidence of complications (eg, nonproliferative retinopathy, microalbuminuria [urinary albumin excretion of 30 to 300 mg/d], or changes in nerve conduction), it is extremely uncommon for a child to have significant diabetic microvascular or macrovascular complications. Nonetheless, glycemic control should be maximized in children who have diabetes to minimize their risk of long-term complications as they age.

Clinical trials, including the Diabetes Control and Complications Trial (DCCT), have demonstrated that the lower the hemoglobin A1c (HbA1c) that a patient maintains, reflecting a lower average blood glucose concentration, the lower the risk of microvascular complications. An improvement in HbA1c of 1% (reflecting a decrease in mean glucose concentrations of 30 to 35 mg/dL [1.67 to 2.9 mmol/L]) decreases the risk of long-term complications by approximately 20% to 50%.

There is no threshold for this effect; that is, a lower HbA1c always is better in terms of lowering the risk of long-term complications. However, the absolute risk reduction is less at lower HbA1c values, and lower average glucose values increase the risk of the acute complications of hypoglycemia. Therefore, diabetes management involves a balancing of the long-term benefit of lowering the average glucose concentration with avoiding the acute complication of hypoglycemia.

Hypoglycemia

Hypoglycemia, a blood glucose concentration less than 60 mg/dL (3.3 mmol/L), occurs frequently in children treated for type 1 diabetes. It is caused by the inability to match the minute-to-minute changes in insulin requirements with current therapy, resulting in periods when insulin action exceeds insulin requirements. Patients who have lower average blood glucose concentrations may have more frequent episodes of hypoglycemia. The severity of hypoglycemic symptoms depends on both the degree of hypoglycemia and the rapidity of its development. The adrenergic symptoms of hypoglycemia include sweating, trembling, hunger, and palpitations; the neuroglycopenic symptoms include headache, light-headedness, dizziness, diplopia, and confusion. With severe hypoglycemia, coma and seizures can occur.

Mild-to-moderate hypoglycemia is treated by ingesting 10 to 15 g of glucose (eg, 4 oz of juice or nondiet soft drink). Hypoglycemia in infants and young children and moderate reactions resulting in confusion in older children require that caregivers, teachers, coaches, and others be prepared to assist in the recognition and treatment of hypoglycemia. Severe reactions require treatment with intramuscular or subcutaneous glucagon (1 mg, except for infants <10 kg, in whom 0.5 mg is given). Because hypoglycemia can occur away from home, a source of glucose to treat it (eg, a tube of cake frosting) and a glucagon emergency kit always should be available.

Ketonemia/Ketonuria and Sick-day Management

The presence of ketones in the urine or blood indicates significant insulin deficiency; urine ketones never should be present in measurable amounts, and blood ketone concentrations should not be elevated in a patient who has type 1 diabetes. The presence of urine or blood ketones should be assessed whenever there is persistent, significant hyperglycemia (eg, blood glucose >250 mg/dL [13.9 mmol/L] in spite of the administration of corrective doses of insulin). Urine or blood ketones also should

be tested whenever the child feels ill, particularly with nausea and vomiting.

Aggressive treatment with additional insulin is necessary once ketosis develops to prevent deterioration into DKA. For a patient whose diabetes is managed with an insulin pump, insulin doses to correct persistent hyperglycemia or ketosis should be given by injection with needle and syringe because pump malfunction is a possible cause of the insulin deficiency. Rapid-acting insulin at doses of 10% to 20% of the total daily requirement should be given every 3 to 4 hours until the ketones are cleared. Care must be taken to avoid causing hypoglycemia in a child who is not able to take sufficient caloric intake because of illness.

Management of diabetes during even simple illnesses can be challenging and more so in illnesses that interrupt oral intake. Although uncertain oral intake puts the patient at risk for hypoglycemia from insulin therapy, insulin treatment must be continued to prevent deterioration into DKA. Indeed, total insulin requirements may increase during illness because of the insulin-antagonizing effects of inflammation and stress hormones. Management of diabetes during an illness usually requires guidance from the patient's diabetes team. Basal insulin should be continued, generally at the usual dose but sometimes at a slightly decreased dose based on blood glucose concentrations. Blood glucose and ketones should be measured frequently (at least every 3 to 4 h). Extra fluids are given to maintain hydration, which also helps excrete excess glucose and ketoacids. If solid foods cannot be eaten, sugar-containing foods such as soda, juice, gelatin dessert, and popsicles can be given to maintain some caloric intake and prevent hypoglycemia. During some illnesses, the usual daily insulin doses, adjusted for intake and glucose concentrations, can be continued. For illnesses in which oral intake is more disrupted, when ketones have developed, or for more significant illnesses, it may be best to treat with more frequent, small doses of insulin; typical doses may be 5% to 10% of the total daily dose every 3 to 4 hours, increasing to 10% to 20% of the total daily dose every 3 to 4 hours if ketones are present.

Persistent vomiting, or a refusal or inability to take fluids or food orally, requires an emergency department or office visit. Glucagon must be available to treat hypoglycemia during an illness. The usual dose is administered for significant hypoglycemia. Because such doses of glucagon frequently cause significant nausea and vomiting, further compromising the ability to ingest food, smaller doses may be more effective for less severe hypoglycemia due to poor intake: 10 mcg/year of age (min-

imum 20 mcg, maximum 150 mcg); if there is no response in 30 minutes, a repeat at twice the dose can be attempted.

DKA

Details on the presentation and management of DKA will be discussed in a subsequent article. Briefly, DKA is a state of metabolic decompensation that results from profound insulin deficiency. DKA is the most common cause of death in children who have type 1 diabetes and is associated with a significant risk of morbidity. Early identification and treatment are key to minimizing the risks. For a child who is not known to have diabetes, the diagnosis of DKA must be considered with the presentation of vomiting and dehydration, particularly in the presence of an altered sensorium or in the absence of other indicators of a viral infection (such as fever and diarrhea). Diabetes mellitus always should be considered when there is a preceding history of polydipsia and polyuria. For a child who has a known diagnosis of diabetes mellitus, ketones should be measured when the child is significantly ill, if there is vomiting, or if there is persistent hyperglycemia. During a ketotic illness, referral for medical care (rather than continued home management) should be considered if the patient begins to vomit. Medical attention is necessary if the patient has deep respirations or is unable to stand.

Management

Goals of Treatment

Treatment goals in type 1 diabetes are to achieve as close to metabolic normalcy as current technology allows, avoid acute complications, minimize the risk of long-term micro- and macrovascular complications, and assist the child and family in achieving normal psychological maturity and independence.

Patients and their families should be seen by the diabetes team about every 3 months to review goals, glycemic control, and acute complications occurring in the interval between visits (and review strategies to avoid recurrences) as well as to screen for complications and comorbidities.

Management Choices

Independent self-management of diabetes is fundamental and important. Children and parents who are well educated about diabetes and its management can make independent decisions about care, which enhances independence, self-esteem, and feelings of control and mastery. Most day-to-day decisions about hypoglycemia, hyperglycemia, ketonuria, illnesses, unusual eating

schedules, events, and activities are handled by knowledgeable families.

The choice of insulin regimen should consider the needs, preferences, and resources of the individual and the family. The diet (meal plan) should be designed using sound nutritional principles but also should consider the individual's and family's habits and food preferences. The diabetes regimen can be adapted to allow children who have type 1 diabetes to participate in any activities appropriate for their age and interest.

Insulin

At diagnosis, patients who have diabetes have some remaining beta cells. The function of these cells can improve with removal of the toxic effect of hyperglycemia on beta cells. Thus, insulin requirements often decline temporarily 1 to 3 months after diagnosis. During this honeymoon period, dose requirements may drop to less than 0.5 units/kg per day. The honeymoon period lasts several months, occasionally 12 months or more. Ultimately, however, most patients who have type 1 diabetes have no significant insulin production. Except during the honeymoon period, most preadolescent children need about 0.5 to 1.0 units/kg per day. Adolescents usually need about 0.8 to 1.2 units/kg per day. This increased need is due to increased insulin resistance during puberty.

All insulin now is manufactured by recombinant DNA technology and is based on the amino acid sequence of human insulin. Three rapid-acting insulin analogs are available: lispro (Humalog[®], Eli Lilly, Indianapolis, Ind.), aspart (NovoLog[®], Novo-Nordisk, Princeton, NJ), and glulisine (Apidra[®], Sanofi-Aventis, Bridgewater, NJ). These insulins are absorbed and cleared more rapidly than regular insulin, more closely mimicking pancreatic insulin secretion. They can be used effectively when given after a meal to children whose food intake is unpredictable.

Regular insulin is short-acting and is used in intravenous infusion to treat DKA. Neutral protamine Hagedorn (NPH) is intermediate in peak and duration of action. Detemir (Levemir[®], NovoNordisk, Princeton, NJ) can be considered either intermediate- or long-acting, with time of action based on dose. Gargine (Lantus[®], Sanofi-Aventis, Bridgewater, NJ) is a peakless analog that has a duration of action of about 20 to 24+ hours. See Table 2 for insulin pharmacodynamics.

With the advent of insulin analogs, many options for insulin regimens now are possible. Split/mixed regimens are the basic two- or three-injection regimens based on intermediate insulin (NPH). Most children and adoles-

Table 2. Timing of Action of Available Insulins*

	Onset (h)	Peak (h)	Duration (h)
Lispro, Aspart, Glulisine	0.25	0.5 to 1.0	3 to 4
Regular	0.5 to 1.0	2 to 3	4 to 6
NPH	2 to 4	6 to 10	14 to 16
Detemir	Slow	6 to 8	6 to 24 [†]
Glargine	2 to 3	no peak	20 to 24

*Times are approximate.
[†]Dose-related.
 Several different mixes are available that combine different percentages of short- or rapid-acting insulin with intermediate-acting insulin.
 NPH=neutral protamine Hagedorn

cents require at least two injections per day of short- and intermediate-acting insulin to achieve satisfactory metabolic control; the injections are administered shortly before breakfast and dinner. During the honeymoon period, one injection per day may be satisfactory for control for some patients. Except for this period, achieving control with a single daily injection is nearly impossible. Absorption may vary from different injection sites and is more rapid in exercised sites and at higher temperatures. Injection into hypertrophied sites may slow absorption.

Split/mixed regimens use, for example, NPH and regular insulin at breakfast and again at dinner. The total dose is split into two injections, each being a mix of NPH and regular. A variation of this regimen is to split the evening dose into regular insulin given at dinner and NPH given at bedtime. The peak actions of insulin used in split/mixed regimens do not correlate well with usual mealtimes and with nutrient absorption. Therefore, ele-

vated between-meal insulin concentrations create a need for snacks to avoid hypoglycemia and can increase the risk of nocturnal hypoglycemia. Most split/mix regimens now use rapid-acting insulin in place of regular insulin. As with regular insulin, rapid-acting insulins can be mixed with NPH to provide both insulins in a single injection. The use of rapid-acting insulin decreases the problem of between-meal insulin peaks. However, the delayed and sometimes variable

peak of NPH poses a significant challenge to achieving glycemic targets without causing hypoglycemia when using split/mixed regimens.

When split/mixed regimens are used, patients usually need about two thirds of their total dose in the morning and one third in the evening. The doses usually are split between one-third regular/rapid-acting insulin and two-thirds NPH to one-half/one-half (Table 3). More regular/rapid-acting insulin may be required in the morning because of the dawn phenomenon, which is caused by normal nocturnal increases in some counter-regulatory hormones that lead to less insulin sensitivity in the early morning.

Basal/bolus regimens aim to achieve more physiologic insulin concentrations with less between-meal insulin action. The basal insulin provides baseline or fasting insulin needs; the bolus doses provide insulin to cover food requirements and to correct hyperglycemia. The basal insulin is provided by either rapid-acting insulin given with the basal rate of an insulin pump or with once- or twice-daily injections of detemir or glargine. (Note that unlike NPH insulin, detemir and glargine cannot be mixed with any other insulin, necessitating their administration as separate injections.) The bolus insulin is provided by acute doses of rapid-acting insulin, either through injections or through bolus doses given by an insulin pump.

Starting dose calculations for basal/bolus regimens are shown in Table 4. The doses are based on empiric formulas, and modifications can be made once responses to starting doses are assessed. Basal

Table 3. Example of Split/mixed Insulin Regimen*

Morning (before breakfast): 16 NPH		
Before dinner or at bedtime: 6 NPH		
Sliding scale regular or rapid-acting dose:		
Blood Glucose Concentration (mg/dL) (mmol/L)	Breakfast	Dinner
<50 (2.8)	6	4
50 to 100 (2.8 to 5.6)	7	5
100 to 150 (5.6 to 8.3)	8	6
150 to 200 (8.3 to 11.1)	9	7
200 to 250 (11.1 to 13.9)	10	8
250 to 300 (13.9 to 16.7)	11	9
>300 (16.7)	12	10

*For a 40-kg child on a diet that has a fixed number of carbohydrate grams per meal (60 for meals and 30 for snacks).
 NPH=Neutral protamine Hagedorn

Table 4. Example of a Basal/Bolus Regimen*

Total daily insulin dose=32 units (0.8 units/kg)
Basal insulin=50% of total daily dose=16 units are given as either 16 units glargine per day OR 0.6 units/h rapid-acting insulin (lispro, aspart, or glulisine) as pump basal rate.
Bolus doses: Insulin-to-carbohydrate ratio for meals and snacks: 450 to 500 divided by total insulin dose (450 to 500/32=14 to 15). Use 1 unit per 15 g carbohydrate to start.
Correction factor: 1800 rule=1,800 divided by total insulin dose (1,800/32=56). Use 1 unit per 60 blood glucose points (or 0.5 units per 30 blood glucose points) above target. Target might be 120 in the daytime and 150 at night.

*For a 40-kg child on a diet that does not have a fixed number of carbohydrates.

requirements usually are about 50% of total daily insulin needs. Bolus doses have two parts to the dose: the amount of insulin needed to cover the carbohydrates in the meal and the amount of insulin needed to correct for a blood glucose concentration outside of the target range. The insulin-to-carbohydrate ratio, which may differ for each patient and for different times of day, is the insulin requirement for each gram of carbohydrate in a meal.

The correction or sensitivity factor is how much the individual patient's blood glucose values fall when given 1 unit of insulin. Thus, the premeal bolus dose equals the insulin-to-carbohydrate ratio multiplied by the grams of carbohydrate to be eaten *plus* the insulin sensitivity factor multiplied by the amount that the blood glucose needs to fall from the preprandial value to reach the target range. Target ranges, for example, may be set at 80 to 120 mg/dL (4.4 to 6.7 mmol/L) for daytime and 100 to 150 mg/dL (5.6 to 8.3 mmol/L) at bedtime. When converting a child from a two- or three-injection regimen with NPH to a basal/bolus regimen, the total daily dose is usually lower, and recommendations are to use 50% to 80% of the NPH dose for the initial basal insulin dose, with the lower percentages used for younger children.

An advantage of insulin pumps over glargine or detemir for basal insulin is that pumps have the capability of delivering different basal rates at different times of the day. In addition, pumps allow for the administration of insulin with snacks without additional "needle sticks"; children on injection-based basal bolus regimens may

resist such additional injections. Combinations of pumps and long-acting insulin (by subcutaneous injections) may allow pump users to disconnect for hours for activities such as sports or swimming.

Nutrition Management

Children and adolescents who have type 1 diabetes require a nutritionally balanced diet that has adequate calories and nutrients for normal growth. The recommended diet usually contains 50% to 55% carbohydrate calories, 20% protein, and approximately 30% fat. Most carbohydrate calories should be complex carbohydrates, and the fat portion should emphasize low amounts of cholesterol and saturated fats. For patients using split/mixed insulin regimens, timing of meals is important to minimize blood glucose variability. In addition to the usual three meals, mid-afternoon snacks are necessary because they coincide with the typical peak of the morning NPH insulin dose and with most after-school sports activities. Bedtime snacks are important for most children receiving evening NPH doses. Midmorning snacks are useful in preschool-age children, but most school-age children find such snacks disruptive to their school routine. This snack usually is not recommended after a child begins elementary school.

Occasional treats should be allowed by the diet plan, and patients and families should learn how to adjust insulin doses for times of increased caloric intake, such as holidays and birthdays. For patients using basal/bolus regimens, nearly total flexibility in timing, amount, and content of meals is possible. The ability to achieve such flexibility requires understanding and performance of accurate carbohydrate counting and insulin dose calculation based on an insulin-to-carbohydrate ratio and a correction factor based on blood glucose concentration (Table 4).

Calorie control to avoid obesity is necessary for certain patients. A sense of satiety and a diet that fits with the family's food preferences are necessary for maximum and realistic adherence to dietary recommendations. The diet should be individualized for each child and family.

Some centers have reported an increased frequency of eating disorders, particularly in adolescent girls who have type 1 diabetes. When this condition occurs, its metabolic consequences can be devastating, and aggressive intervention (eg, admission to an eating disorders unit) is indicated.

Nutritional management is complex and guided best by a nutritionist who has expertise in diabetes management. Such guidance is especially critical in sophisticated regimens involving carbohydrate counting.

Exercise

Metabolic control, self-esteem, and body image may be better in the physically fit child. Therefore, physical fitness and regular exercise should be encouraged in all children who have type 1 diabetes. Exercise in a child who has diabetes does require specific attention, however. During periods of exercise, extra calories or lower insulin doses may be needed to prevent hypoglycemia. Some patients have a delayed hypoglycemic response to exercise, sometimes hours later. Blood glucose monitoring to assess the effects of exercise and the response to interventions allows determination of an effective regimen for the individual child. The stress of exercise when metabolic control is poor (eg, during hyperglycemia, especially with ketosis) may worsen metabolic control, so it may be necessary to delay exercise at these times.

Monitoring

Self-monitoring of blood glucose is fundamental to diabetes management. More frequent monitoring has been shown to correlate with improved glycemic control. Glucose meters are small, portable, and accurate, and many have memory storage of several hundred readings. Some meters allow patients to record carbohydrate amounts and insulin doses. The ability to download the information to computers with specialized software programs and to communicate the glucose value from the meter to an insulin pump also is available.

Blood glucose traditionally is monitored before meals, at bedtime, and overnight. Some children also monitor before snacks, especially children receiving bolus insulin with all carbohydrate intake. Basal/bolus regimens require a blood glucose measurement each time the patient ingests any calories to determine what insulin dose to take. Postprandial values can be helpful in assessing whether the selected dose was satisfactory. Many people monitor at least 8 to 10 times per day, more often with sports, when ill, or during periods of metabolic instability. Fasting and preprandial blood glucose readings in the range of 100 to 180 mg/dL (5.6 to 10.0 mmol/L) for preschool-age children, 90 to 180 mg/dL (5.0 to 10.0 mmol/L) for school-age children, and 90 to 130 mg/dL (5.0 to 7.2 mmol/L) for teenagers are reasonable goals. Bedtime or overnight values of 110 to 200 mg/dL (6.1 to 11.1 mmol/L) in preschoolers, 100 to 180 mg/dL (5.6 to 10.0 mmol/L) in school-age children, and 90 to 150 mg/dL (5.0 to 8.3 mmol/L) in teenagers also are reasonable.

New continuous glucose sensors read interstitial glucose concentrations and send the readings every few minutes to a display. Such devices also display rate and

direction of change and alarms. Acceptability of these sensors in children and youth, improvement in metabolic control, and insurance coverage remain to be determined.

Glycated hemoglobin, another name for HbA1c, is an objective value of average blood glucose concentration over approximately the previous 2 months and should be measured regularly, usually every 3 months. Although the ideal goal is to achieve an HbA1c value as close to normal as possible, goals that most patients should achieve vary with age: 7.5% to 8.5% for toddlers and preschoolers (<6 y), less than 8% for school-age children (6 to 12 y), and less than 7.5% for adolescents and young adults (13 to 19 y). However, hypoglycemia often limits the ability to achieve these goals. Indeed, with the limitations of current insulins and methods of administration, such target levels often cannot be reached, especially in adolescents. The high risk and vulnerability of young children to hypoglycemia are the reasons that blood glucose values and HbA1c goals are higher for younger children.

Urine or blood ketones also should be monitored when the blood glucose values are elevated (eg, > 250 to 300 mg/dL [13.9 to 16.7 mmol/L]), when children have a fever, when they feel nauseated or are vomiting, or when they simply are not feeling well. Such monitoring is important in achieving the goal of aborting DKA episodes by treating early ketosis.

Education

Living with and managing diabetes is complex and demanding and requires initial and ongoing education, which is fundamental to diabetes management and control. Patients and families need to understand all aspects of diabetes, including acute and long-term complications. They must understand details of insulin action, including duration and timing and dose adjustments, injection and insertion techniques, electronics and mechanics of insulin pumps, dietary information, blood glucose monitoring and interpretation, and urine ketone checks and appropriate interventions. They must gain skills in integrating the demanding clinical regimen into their schedules so they can achieve emotional stability and ongoing psychological growth.

Education about diabetes must be appropriate to the child's age and the family's educational background, and it must be ongoing. Responsibility for diabetes self-care skills (eg, insulin injections) should be shifted gradually from parent to child and when the child shows interest and readiness to take responsibility. Premature shifting of responsibility may result in deterioration of metabolic

control. Management of diabetes involves the whole family because the life of the entire family is affected by having a child who has type 1 diabetes. Sharing responsibilities and attending support groups and camps for children who have type 1 diabetes can help with psychological adjustment.

A diabetes management team, including a physician, nurse educator, dietitian, and mental health professional, handles teaching about diabetes management best. Excellent comprehensive educational manuals for children and families are available, and several comprehensive Web sites are exceptional (see selected resources at the end of the article). Diabetes education is life-long, for patients, families, and the diabetes team.

Chronic Complications and Comorbidities

Associated Autoimmune Disease

Associated autoimmune disease, particularly thyroid dysfunction, occurs with greater frequency in individuals who have type 1 diabetes. Thyroid-stimulating hormone (TSH) should be measured shortly after diagnosis and may be measured subsequently every 1 to 2 years. TSH also should be measured whenever any thyroid-related signs or symptoms occur. Thyroxine concentrations and thyroid antibodies also may be assessed. Although rare, autoimmune adrenal hypofunction can occur, and symptoms to suggest this disorder should prompt appropriate testing.

Celiac disease also occurs more frequently in children who have type 1 diabetes; all patients should be screened for this disorder at least once and any time poor growth and gastrointestinal symptoms occur. Tissue transglutaminase and antiendomysial antibodies are more sensitive and specific than antigliadin antibodies. Also, because these are immunoglobulin A (IgA) antibodies, it is important to assure that the individual patient is not IgA-deficient by measuring IgA concentrations.

Growth Disturbance

Linear growth is affected negatively by poor diabetic control. Decreased growth velocity, crossing percentiles downward for height and weight, eventual short stature, and delayed skeletal and sexual maturation are associated with chronic undertreatment with insulin. An extreme form of this effect—the Mauriac syndrome or diabetic dwarfism—occurs rarely and usually is associated with hepatomegaly. Height and weight should be measured at every appointment and plotted on growth curves so deviations from normal velocities can be detected early. Alternatively, treatment with excessive insulin doses often leads to excessive weight gain, causing the weight

curve to cross percentiles upward. Maintenance of normal growth curves for height and weight is an important goal of diabetes management.

Retinopathy

Retinopathy usually is not seen before 5 to 10 years of diabetes duration. Recommendations from the American Diabetes Association are for the first ophthalmologic examination to occur once the child is at least 10 years old and has had diabetes for 3 to 5 years. Yearly follow-up examinations generally are recommended. Poor metabolic control, elevated blood pressure, smoking, albuminuria, and elevated lipid values are risk factors for retinopathy. Diabetes duration and pregnancy also are associated with increased risk.

Nephropathy

A significant minority of patients who have type 1 diabetes eventually develops end-stage renal disease, necessitating dialysis or transplantation. All patients who have type 1 diabetes should be monitored by urine microalbumin determination at least annually beginning after the child is 10 years old and has had diabetes for 5 years. Because hypertension accelerates the progression of nephropathy, blood pressure should be monitored several times a year, and hypertension should be treated aggressively. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are recommended for treatment of hypertension. If hypertension, overt proteinuria, or elevation in serum creatinine or urea nitrogen values is found, monitoring of renal function several times each year and consultation with a nephrologist are warranted. Microalbuminuria (30 to 299 mg of albumin per gram of creatinine on spot urine) is a marker for early nephropathy. Two of three urine specimens that have elevated values, measured on different days, are needed for confirmation. Whether using angiotensin-converting enzyme inhibitors in normotensive individuals prevents or retards nephropathy is not known. Patients should avoid other risk factors for nephropathy, such as smoking.

Neuropathy

Symptomatic diabetic neuropathy, peripheral or autonomic, is uncommon in children and adolescents who have type 1 diabetes. Changes in nerve conduction, however, may be seen after 4 to 5 years of having diabetes. Overall, neuropathy is a common type 1 diabetes complication, and its frequency increases with the duration of disease and degree of hyperglycemia. Improve-

ments in glycemic control may improve neuropathic symptoms.

Macrovascular Complications/Lipids

Patients who have type 1 diabetes tend to have coronary artery, cerebrovascular, and peripheral vascular disease more often, at an earlier age, and more extensively than the nondiabetic population. Hypertension, elevated blood lipid concentrations, and cigarette smoking are other risk factors for developing macrovascular complications. Risk factors should be analyzed, including lipid panels, blood pressure measurements, and determination of smoking status, and treatment instituted as indicated. A strong admonition against smoking and referral to an appropriate program for patients who already are smokers is crucial. Studies continue to show that lower low-density lipoprotein (LDL) values are beneficial in lowering the risk of vascular disease, and recommendations continue to evolve. Screening with fasting lipid measurements should begin in children at age 12 years if there is no concerning family history and at diagnosis (after establishing metabolic control) when there is a positive family history for lipid abnormalities or early cardiovascular events.

Current recommendations are to treat children older than age 10 years who have LDL cholesterol concentrations at or above 160 mg/dL (4.14 mmol/L) and to consider treatment if the LDL value is at or above 130 mg/dL (3.37 mmol/L) if other risk factors are present. The goal is to achieve an LDL value below 100 mg/dL (2.59 mmol/L). Although bile acid sequestrants may be recommended as the first treatment in children, they are poorly tolerated, and effective therapeutic data are lacking. Thus, statins should be considered, with appropriate monitoring. Of course, dietary counseling and blood glucose control are important parts of management.

Summary

1. Based on strong research evidence, type 1 diabetes is an autoimmune disease that has an underlying genetic predisposition (Jahromi, 2007).
2. Based on strong research evidence, risks of diabetes complications are decreased with improved glycemic

control (lower HbA1c) (DCCT Research Group, 1993).

3. Based on some research data and consensus opinion, insulin analogs, glucose monitoring, and delivery device technology have improved management of this disease and quality of life of affected individuals (Silverstein, 2005).

Suggested Reading

- American Diabetes Association. Management of dyslipidemia in children and adolescents with diabetes. *Diabetes Care*. 2003;26:2194–2197
- Chase HP, Dixon B, Pearson J, et al. Reduced hypoglycemic episodes and improved glycemic control in children with type 1 diabetes using insulin glargine and NPH. *J Pediatr*. 2003;143:737–740
- DCCT Research Group. The effect of intensive diabetes treatment on long-term complications in adolescents with IDDM: the DCCT. *J Pediatr*. 1994;125:177–188
- DCCT Research Group. The effect of intensive diabetes treatment on the development and progression of long-term complications in IDDM: the DCCT. *N Engl J Med*. 1993;329:977–986
- Expert Committee on the Diagnosis and Classification of Diabetes. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2007;S1:S42–S47
- Jahromi MM, Eisenbarth GS. Cellular and molecular pathogenesis of type 1A diabetes. *Cell Mol Lif Sci*. 2007;64:865–872
- Lueder GT, Silverstein J; American Academy of Pediatrics Section on Ophthalmology and Section on Endocrinology. Screening for retinopathy in the pediatric patient with type 1 diabetes. *Pediatrics*. 2005;116:270–273
- Silverstein J, Klingensmith G, Copeland K, et al; American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28:186–212
- White NH, Cleary PA, Dahma W, et al. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the DCCT. *J Pediatr*. 2001;139:804–812

Web Sites

- American Diabetes Association: www.diabetes.org
- Children With Diabetes: www.childrenwithdiabetes.com
- Diabetes TrialNet: www.diabetestrialnet.org/
- Juvenile Diabetes Research Foundation: www.jdrf.org/
- Immune Tolerance Network: www.immunetolerance.org/
- International Society for Pediatric and Adolescent Diabetes diabetes guidelines: www.ispad.org

PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

1. The percentage of beta cells that must be destroyed before glucose and lipid homeostasis become impaired is closest to:
 - A. 20%.
 - B. 40%.
 - C. 60%.
 - D. 80%.
 - E. 100%.
2. A 1% improvement in the HbA1c values is likely to reduce the risk of long-term complications by approximately:
 - A. 1% to 5%.
 - B. 10% to 19%.
 - C. 20% to 50%.
 - D. 60% to 80%.
 - E. 90% to 95%.
3. Target HbA1c values vary with age. In the adolescent/young adult, the ideal goal is less than:
 - A. 8.5%.
 - B. 8.0%.
 - C. 7.5%.
 - D. 7.0%.
 - E. 6.5%.
4. Among the following acute complications of type 1 diabetes, which appears to be the *most* important in determining the risk of long-term complications?
 - A. Dehydration.
 - B. Glucosuria.
 - C. Hyperglycemia.
 - D. Hypoglycemia.
 - E. Ketoacidosis.
5. Which of the following is a *false* statement regarding the pathogenesis and epidemiology of type 1 diabetes?
 - A. In spite of the increase in pediatric obesity, type 1 diabetes remains the most common form of diabetes in children.
 - B. Most patients who have type 1 diabetes have a similarly affected family member.
 - C. Not all individuals who have measurable antibodies against B-cell antigens (such as islet cell autoantibodies) develop type 1 diabetes.
 - D. The risk of type 1 diabetes is linked to the major histocompatibility complex.
 - E. The terms "regular" and "rapid-acting" refer to different kinds of insulin.

Type 1 Diabetes Mellitus in Pediatrics

David W. Cooke and Leslie Plotnick

Pediatr. Rev. 2008;29;374-385

DOI: 10.1542/pir.29-11-374

Updated Information & Services

including high-resolution figures, can be found at:
<http://pedsinreview.aappublications.org/cgi/content/full/29/11/374>

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

Endocrine Disorders

http://pedsinreview.aappublications.org/cgi/collection/endocrine_disorders

Metabolic Disorders

http://pedsinreview.aappublications.org/cgi/collection/metabolic_disorders

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:

<http://pedsinreview.aappublications.org/misc/Permissions.shtml>

Reprints

Information about ordering reprints can be found online:

<http://pedsinreview.aappublications.org/misc/reprints.shtml>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

