

SECTION 6 *Diabetes Mellitus in Children*

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Chapter 583

Diabetes Mellitus

583.1 Introduction and Classification

Diabetes mellitus (DM) is a common, chronic, metabolic syndrome characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are divided into those caused by deficiency of insulin secretion due to pancreatic β -cell damage (type 1 DM), and those that are a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β -cell impairment (type 2 DM). Type 1 DM is the most common endocrine-metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Individuals with type 1 DM confront serious lifestyle alterations that include an absolute daily requirement for exogenous insulin, the need to monitor their own glucose control, and the need to pay attention to dietary intake. Morbidity and mortality stem from acute metabolic derangements and from long-term complications (usually in adulthood) that affect small and large vessels resulting in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities. The acute clinical manifestations are due to hypoinsulinemic hyperglycemic ketoacidosis. Autoimmune mechanisms are factors in the genesis of type 1 DM; the long-term complications are related to metabolic disturbances (hyperglycemia).

DM is not a single entity but rather a heterogeneous group of disorders in which there are distinct genetic patterns as well as other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance. A classification of diabetes and other categories of glucose intolerance is presented in Table 583-1. Three major forms of diabetes and several forms of carbohydrate intolerance are identified.

Type 1 Diabetes Mellitus. Formerly called insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes, type 1 DM is characterized by low or absent levels of endogenously produced insulin and dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of type 1 DM. The natural history includes preketotic, non-insulin-dependent phases both before and after the initial diagnosis. The onset occurs predominantly in childhood, with median age of 7 to 15 yr, but it may present at any age. Type 1 DM is characterized by autoimmune destruction of pancreatic islet β cells. Both genetic susceptibility and environmental factors contribute to the pathogenesis of type. Susceptibility to type 1 DM is genetically controlled by alleles of the major histocompatibility complex (MHC) class II genes expressing human leukocyte antigens (HLAs). It is also associated with autoantibodies to islet cell cytoplasm (ICA), insulin (IAA), antibodies to glutamic acid decarboxylase (GADA or GAD65), and ICA512 (IA2). Type 1 DM is associated with other autoimmune diseases such as thyroiditis, celiac disease, multiple sclerosis, and Addison disease. In some children and adolescents with apparent type 1 DM, the β -cell destruction is not immune-mediated. This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β -cell destruction,

TABLE 583-1. Etiologic Classifications of Diabetes Mellitus

Type I diabetes* (β -cell destruction, usually leading to absolute insulin deficiency)	<i>Drug- or chemical-induced</i>
Immune mediated	Vacor
Idiopathic	Pentamidine
	Nicotinic acid
	Glucocorticoids
	Thyroid hormone
	Diazoxide
	β -Adrenergic agonists
	Thiazides
	Dilantin
	β -Interferon
	Others—cyclosporine, tacrolimus
Type II diabetes* (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)	<i>Infections</i>
	Congenital rubella
	Cytomegalovirus
	Others—hemolytic uremic syndrome
Other specific types	<i>Uncommon forms of immune-mediated diabetes</i>
<i>Genetic defects of β-cell function</i>	"Stiff-man" syndrome
Chromosome 12, HNF-1 α (formerly MODY-3)	Cytomegalovirus
Chromosome 7, glucokinase (formerly MODY-2)	Others
Chromosome 20, HNF-4 α (formerly MODY-1)	
Mitochondrial DNA	
Others	
<i>Genetic defects in insulin action</i>	
Type A insulin resistance	
Leprechaunism	
Rabson-Mendenhall syndrome	
Lipomatrophic diabetes	
Others	
<i>Diseases of the exocrine pancreas</i>	
Pancreatitis	
Trauma, pancreatectomy	
Neoplasia	
Cystic fibrosis	
Hemochromatosis	
Fibrocystic pancreatopathy	
Pancreatic resection	
Others	
<i>Endocrinopathies</i>	
Acromegaly	
Cushing disease	
Glucagonoma	
Pheochromocytoma	
Hyperthyroidism	
Somatostatinoma	
Aldosteronoma	
Others	
	Gestational diabetes mellitus
	Neonatal diabetes mellitus
	Transient—without recurrence
	Transient—recurrence 7–20 yr later
	Permanent from onset

*Patients with any form of diabetes may require insulin treatment at some stage of the disease. Such use of insulin does not, of itself, classify the patient.

which include drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and ionizing radiation. These individuals may present with ketoacidosis but have extensive periods of remission with variable insulin deficiency, similar to patients with type 2 DM.

Type 2 Diabetes Mellitus. The children and adolescents with this type of diabetes are usually obese but are not insulin-dependent and infrequently develop ketosis. Some may develop ketosis during severe infections or other stresses and may then need insulin for correction of symptomatic hyperglycemia. This category includes the most prevalent form of diabetes in adults, which is characterized by insulin resistance and often a progressive defect in insulin secretion. This type of diabetes was formerly known as adult-onset diabetes mellitus, non-insulin-dependent diabetes mellitus (NIDDM), or maturity-onset diabetes of the young (MODY).

The presentation of type 2 DM is typically more insidious than that with type 1 DM. In contrast to patients with type 1 DM who are usually ill at the time of diagnosis, children with type 2 DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or incidental finding of glycosuria during routine physical examination. A history of polyuria and polydipsia is relatively uncommon in these patients. The incidence of type 2 DM in children has increased by more than 10-fold in many diabetes centers, in part as a result of the epidemic of childhood obesity. Pediatric type 2 DM may account for as many as 30% of the new cases of diabetes, especially in obese African and Mexican American adolescents. *Acanthosis nigricans* (dark pigmentation of skin creases/flexural areas), a sign of insulin resistance, is present in the majority of patients with type 2 DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis (see Chapter 642). However, the serum insulin elevation is usually disproportionately lower than that of age-, weight-, and sex-matched nondiabetic children and adolescents, suggesting a state of insulin insufficiency. In some individuals, it may represent slowly evolving type 1 DM.

In some children with strong family history of type 2 DM, impaired glucose tolerance may occur in a pattern implying dominant inheritance. This pattern of diabetes has been termed *maturity-onset diabetes of the young* (MODY) and may require insulin treatment. In MODY, there is no apparent autoimmune destruction of β cells and no association with HLAs. This subclass of type 2 DM consists of specific genetic disorders involving mutations in the gene encoding pancreatic β -cell and liver glucokinase (GK) or in the nuclear transcription factors hepatocyte nuclear factor (HNF)-4 α or hepatic nuclear factor (HNF)-1 α . A defect in the gene regulating glucose transport into the pancreatic β cell, GLUT-2 transporter, may be responsible for other forms of type 2 DM. The genetic basis of type 2 DM also includes defects in glycogen synthase, insulin receptors, Rad (Ras associated with diabetes), and possibly apolipoprotein C-III.

Other Specific Types of Secondary Diabetes. Examples include diabetes secondary to exocrine pancreatic diseases (e.g., cystic fibrosis), endocrine diseases other than pancreatic diseases (e.g., Cushing syndrome), and ingestion of certain drugs or poisons (e.g., the rodenticide Vacor). Certain genetic syndromes, including those with abnormalities of the insulin receptor, also are included in this category. There are no associations with HLAs, autoimmunity, or islet cell antibodies among the entities in this subdivision.

Table 583–2 details the current criteria for the diagnosis of DM. It should be noted that a fasting blood glucose that exceeds 126 mg/dL (7.0 mM) is the accepted criterion for diagnosing diabetes.

TABLE 583–2. Diagnostic Criteria for Impaired Glucose Tolerance and Diabetes Mellitus

Impaired Glucose Tolerance (IGT)	Diabetes Mellitus (DM)
Fasting glucose 110–125 mg/dL (6.1–7.0 mmol/L)	Symptoms* of DM plus random plasma glucose \geq 200 mg/dL (11.1 mmol/L)
	or
2-hr plasma glucose during the OGTT <200 mg/dL (11.1 mmol/L) but \leq 140 mg/dL	Fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L)
	or
	2-hr plasma glucose during the OGTT \geq 200 mg/dL

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.

OGTT, oral glucose tolerance test.

From Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1999; 20(Suppl 1):S5.

Impaired Glucose Tolerance. The term *impaired glucose tolerance* (IGT) refers to a metabolic stage that is intermediate between normal glucose homeostasis and diabetes. A fasting glucose concentration of 109 mg/dL (6.1 mmol/L) is the upper limit of “normal.” This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications.

Many individuals with IGT are euglycemic in their daily lives and may have normal or nearly normal glycated hemoglobin levels. Individuals with IGT often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test.

In the absence of pregnancy, IGT is not a clinical entity but rather a risk factor for future diabetes and cardiovascular disease. This may be observed as an intermediate stage in any of the disease processes listed in Table 583–1. IGT is associated with the *insulin resistance syndrome* (also known as syndrome X or the metabolic syndrome), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low-high-density lipoprotein type, or both, and hypertension. Insulin resistance is directly involved in the pathogenesis of type 2 DM. IGT appears as a risk factor for this type of diabetes at least in part because of its correlation with insulin resistance. The diagnostic criteria for IGT are presented in Table 583–2.

583.2 Type 1 Diabetes Mellitus (Immune Mediated)

Epidemiology: Genetics and Environment. The incidence of type 1 DM is rapidly increasing in specific regions and shows a trend toward earlier age of onset. The incidence of type 1 DM is highly variable among different ethnic groups. The overall age-adjusted incidence of type 1 DM varies from 0.7/100,000 per year in Karachi (Pakistan) to about 40/100,000 per year in Finland (Fig. 583–1). This represents more than a 400-fold variation in the incidence among about 100 populations analyzed. The increased incidence is seen in nations with a previous low incidence of autoimmune diabetes. For instance, the incidence of type 1 DM in Thailand increased markedly from 0.2/100,000 in 1984–1985 to 1.65/100,000 10 yr later. It is predicted that the overall incidence of type 1 DM will be about 40% higher in 2010 than in 1997.

Data from Western European diabetes centers suggest that the annual rate increase in type 1 DM incidence is 3–4%, whereas some central and eastern European countries demonstrate a significantly more rapid increase. The rates of increase in type 1 DM incidence as a function of age at onset are 6.3%, 3.1%, and 2.4% in age groups of children 0–4 yr, 5–9 yr, and 10–14 yr, respectively. In the United States, the prevalence of diabetes among school-aged children is about 1.9/1,000. The frequency, however, is highly correlated with increasing age; the range is 1 case/1,430 children at 5 yr of age to 1 in 360 children at 16 yr. Among African Americans, the occurrence of type 1 DM is between one third and two thirds of that seen in American whites. The annual incidence in the United States is about 14.9 new cases/100,000 of the child population. Girls and boys are almost equally affected; there is no apparent correlation with socioeconomic status. Peaks of presentation occur in two age groups: at 5–7 yr of age and at the time of puberty. Nonetheless, a growing number of patients are presenting between 1 and 2 yr of age. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the latter may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth

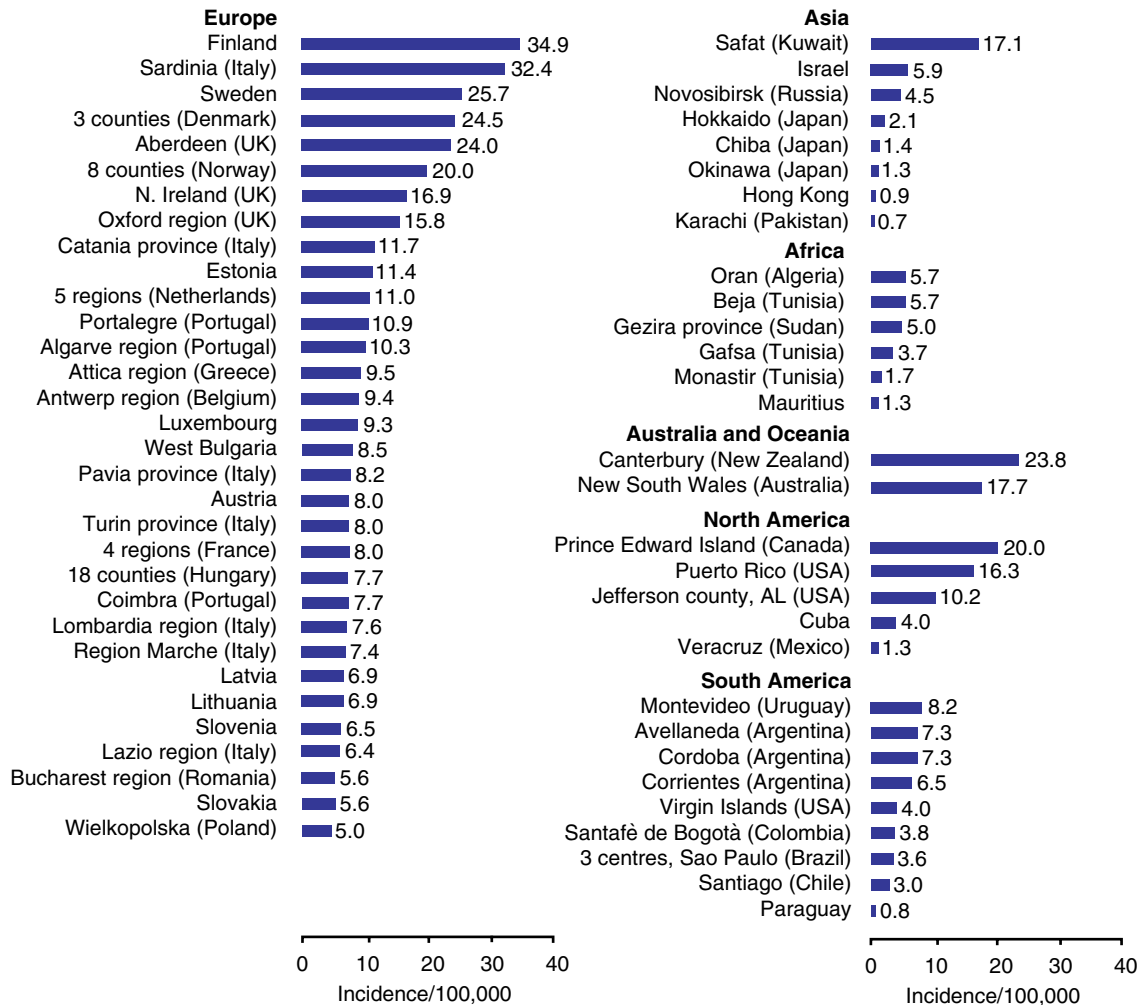


FIGURE 583–1. Incidence rates of type 1 diabetes mellitus by region and country. (From LaPorte RA, et al: The DiaMond Project. *Pract Diabetes Int* 1995;12:93.)

hormone secretion (which antagonizes insulin). These possible cause-and-effect relationships remain to be proved.

GENES. Genes for type 1 DM may provide both susceptibility to, and protection from, the disease. Although many chromosomal loci associated with such activities have been located, few true genes have been identified. The genetics of type 1 DM cannot be classified according to a specific model of inheritance. The most important genes are located within the MHC HLA class II region on chromosome 6p21, formally termed (IDDM1), accounting for about 60% genetic susceptibility for the disease; their specific contribution to the pathogenesis of type 1 DM remains unclear. The importance of the class II haplotypes not only depends on the well-known risk for disease associated with HLA-DR3 and HLA-DR4 but also on additional susceptibility associated with DQ α -chains and DQ β -chains. Inheritance of HLA-DR3 or -DR4 antigens appears to confer a twofold to threefold increased risk for the development of type 1 DM. When both DR3 and DR4 are inherited, the relative risk for the development of diabetes is increased 7–10-fold. Analysis of DNA polymorphisms after digestion by specific restriction endonucleases has revealed further heterogeneity in the HLA-DR region among individuals with and without diabetes despite the possession of both DR3 or DR4 markers, suggesting a yet to be defined “susceptibility” locus within these markers.

In whites, at least one major susceptibility locus may reside in the DQB_1 gene. The homozygous absence of aspartic acid at position 57 of the HLA DQ β -chain (nonAsp/nonAsp) confers an approximately 100-fold relative risk for the development of type 1 diabetes. Those who are heterozygous with a single aspartic acid at position 57 (nonAsp/Asp) are far less likely to acquire diabetes and only marginally more susceptible than individuals who have aspartic acid on both DQ β -chains, that is, homozygous Asp/Asp. Thus, the presence of aspartic acid at one or both alleles of DQ β protects against the development of autoimmune diabetes. Indeed, the incidence of type 1 DM in any given population appears to be proportional to the gene frequency of nonAsp alleles in that population. In addition, arginine at position 52 of the DQ β -chain confers marked susceptibility to type 1 DM. Position 57 of the DQ β and position 52 of DQ β are at critical locations of the HLA molecule that permit or prevent antigen presentation to T-cell receptors and activate the autoimmune cascade. However, type 1 DM seems unique among autoimmune diseases, in that, in addition to forming susceptibility, certain MHC haplotypes provide significant protection. The HLA-DRB1*0301, HLA-DRB1*0401, HLA-DQB1*0302, and HLA-DQA1*0301 alleles of MHC (IDDM1) confer high-risk susceptibility in humans, whereas other alleles such as HLA-DRB1*0403, HLA-DQB1*0602, and HLA-DQA1*0102 are negatively associated with type 1 DM and may confer resistance.

The observation that 20% of individuals from Europe or the United States carry protective HLA-DR2 haplotype, yet fewer than 1% of children with type 1 DM are DR2 (DQB1*0602) positive, signifies the importance of genetics in disease development.

Type 1 DM represents a heterogeneous and polygenic disorder. About 20 non-HLA loci contributing to disease susceptibility have been identified. The function of only two non-HLA loci is known. IDDM2 on chromosome 11p5.5 is a polymorphic region that maps to a variable number of tandem minisatellite repeats (VNTR), with short class I VNTR alleles predisposing to type 1 DM and the longer class III alleles providing dominant protective effect. This locus contributes about 10% toward disease susceptibility. Another locus associated with type 1 DM in some populations is IDDM12 on chromosome 2q33, which maps close to two T-cell markers involved in the T-cell activation: cytotoxic T lymphocyte-associated protein4 (CTLA-4) and CD28. Studies in Italian and Spanish families have shown that a polymorphism at CTL4 gene (A-G transition at position 49 of exon 1) called G allele, is preferentially transmitted to the affected siblings.

Factors other than pure inheritance of HLA markers or other genes must also be involved in producing diabetes. For example, HLA-DR3 or -DR4 is found in approximately 50% of the general population, and (nonAsp/nonAsp) is found in approximately 20% of nondiabetic whites in the United States, yet the risk for type 1 DM in these subjects is only one tenth of that in an HLA identical sibling of an index case possessing these markers. Even siblings sharing only one haplotype have a 6–10-fold greater risk of development of type 1 DM compared with the normal population. In addition, about 10% of patients with type 1 DM do not possess either HLA-DR3 or -DR4, although most white diabetic patients lack at least one aspartic acid at position 57 of the DQ β chain. The concordance rate among identical twins of whom one has type 1 DM is only 30–50%, suggesting the participation of environmental triggering factors or other genetic factors such as the postnatal selection of certain autoreactive T-cell clones that bear receptors recognizing “self.” This postnatal process occurs within the thymus and implies that identical twins are not identical with respect to the T-cell receptor repertoire they possess.

Type 1 DM among African Americans is associated with the same HLA genes as it is in whites. If a sibling shares both HLA-D haplotypes with an index case, the risk for type 1 DM in that individual is 12–20%; for a sibling sharing one haplotype, the risk is 5–7%; with no haplotypes in common, the risk is only 1–2%. It can be assumed that in whites, the overall risks to siblings is approximately 6% if the proband is younger than 10 yr of age and 3% if the proband is older at the time of diagnosis. The risk to offspring of a diabetic parent is 2–5%, with the higher risk occurring in the offspring of a diabetic father. In African Americans, these risks are only one half to two thirds of those in whites.

ENVIRONMENT. Factors such as infections, chemicals, seasonality, and geographic locations have been suspected of contributing to differences in the incidence and prevalence of type 1 DM in various ethnic populations. No dominant environmental agent or agents responsible for triggering type 1 DM have been uncovered. Environmental risk determinants that have been vigorously investigated can be classified into viral infections, early infant diet, and chemicals.

Viral Infections and Vaccinations. Although the etiologic role of viral infections in human type 1 DM is controversial, coxsackie B3, coxsackie B4, cytomegalovirus, rubella, and mumps can infect human β cells. Only congenital rubella infection is associated with diabetes in later life. It is estimated that 10–12% of patients infected with congenital rubella develop type 1 DM and that up to 40% develop impaired glucose tolerance. The diabetes induced by rubella resembles type 1 DM because it is

associated to HLA-DR3 and/or HLA-DR4 and is mediated by immune responses against β -cell antigens. There has been no convincing correlation between timing of childhood vaccinations and risk of type 1 DM.

Seasonal Factors. Seasonal and long-term cyclic variations occur in the incidence of IDDM. Newly recognized cases appear with greater frequency in the autumn and winter months in the northern and southern hemispheres. Seasonal variations are most apparent in the adolescent years. Attempts to link a pattern of long-term cyclicality with the incidence of mumps or other viral infections have not been successful.

Dietary Factors. Feeding cow's milk to animal models of type 1 DM has been associated with the development of diabetes in these animals. The likely mechanism is the molecular mimicry between a 17-amino acid peptide of the bovine serum albumin and the islet antigen 69. Even though there appears to be a strong relationship between cow's milk consumption and national incidence of diabetes in children, the role of cow's milk in human type 1 DM is controversial. N-nitroso compounds, derived from the conversion of nitrates from dietary vegetables and meat in the gut, have also been involved in the development of diabetes. The role of these compounds as a significant risk factor in the pathogenesis of diabetes remains controversial.

Chemicals. Drugs such as alloxan, streptozotocin (STZ), pentamidine, and Vacor are directly cytotoxic to β cells and cause diabetes in experimental animals and humans. In susceptible animals, multiple subdiabetogenic doses of STZ induce primary β -cell damage and subsequently immune responses against β cells, providing mechanistic evidence that a β -cell insult can elicit specific autoimmunity. Autoimmunity against β cells has also been reported in humans after intoxication with the human rodenticide Vacor.

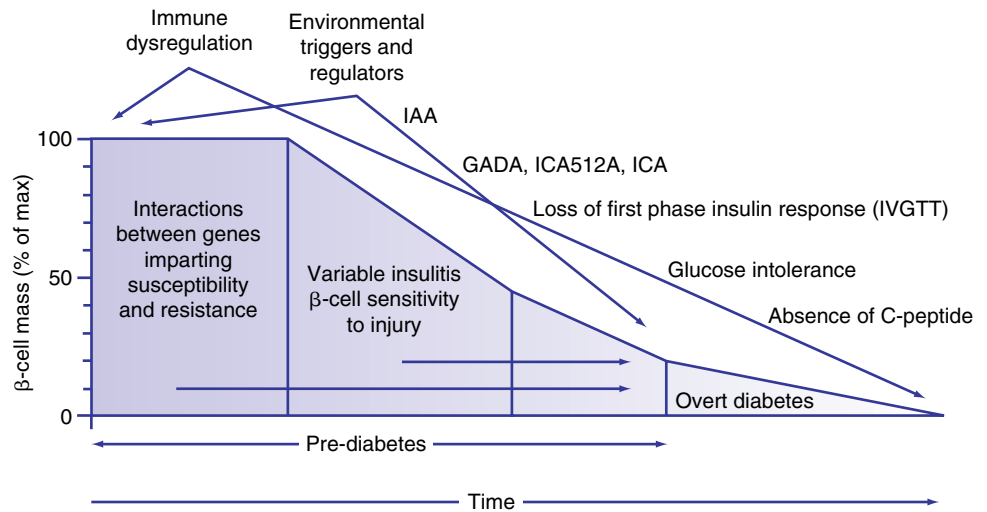
Figure 583–2 summarizes current concepts of the etiology of type 1 DM as an autoimmune disease, with a genetic component inherited through the HLA system, in which autoimmune destruction of β cells is triggered by an as yet unidentified agent. The slope of decline in insulin varies, and the point at which clinical features appear corresponds to an approximately 80% destruction of the insulin secretory reserve. This process may take months to years, usually in adolescent and older patients, and weeks in the very young patient. Higher titers of spontaneous autoinsulin antibodies and islet cell antibodies are characteristic of the more active islet cell destruction typically seen in the younger patient and may prove useful in predicting evolving diabetes.

Environmental agents may serve as modifiers of disease pathogenesis rather than triggers. These include infectious agents, dietary factors, environmental toxins as well as other influencing variables such as sanitation, health care access, and vaccinations. Multiple infections during the 1st yr of life are associated with a decreased risk of type 1 DM. Increased risk has been associated with perinatal infections coupled with a protective effect of preschool daycare with a possible link to the age-dependent modifying effect of infections on the developing immune system. Environmental exposures could act to promote and attenuate disease during different stages of development, with effect dependent on both timing and quantity of encounters.

Pathogenesis

AUTOIMMUNE INJURY. Genetic predisposition and environmental factors lead to initiation of an autoimmune process against the pancreatic islets. It is also assumed that the autoimmune response needs to be sustained and diversified against multiple target proteins (epitope spreading) for prolonged periods of time to overcome protective mechanisms. The autoimmune attack on the pancreatic islets leads to a gradual and progressive destruction of β cells with loss of insulin secretion. It is estimated that, at the onset of clinical diabetes, 80–90% of the pancreatic islets are destroyed. Regeneration of new islets has

FIGURE 583–2. Proposed model of the pathogenesis and natural history of type 1 DM. IVGTT = intravenous glucose tolerance test; GADA = glutamic acid decarboxylase antibody; IAA = insulin autoantibodies; ICA = islet cell antibody. (Adapted from Atkinson MA, Eisenbarth GS: Type 1 diabetes: New perspectives on disease pathogenesis and treatment. *Lancet* 2001; 358:221–9.)



been detected at onset of type 1 DM, and it is thought to be responsible for the honeymoon phase (a transient decrease in insulin requirement associated with improved β -cell function). In young diabetic children, especially those of DR3/DR4 haplotypes, the destruction of β cells is almost complete during the first 3 yr after the onset of hyperglycemia, whereas in older patients the β -cell destruction may take up to 10 yr. These observations indicate that the impairment of β -cell function at the onset of hyperglycemia is the consequence of both β -cell destruction and cytokine-mediated inhibition of insulin secretion. The distinction between β -cell destruction and inhibition of insulin secretion is important, since a fraction of β -cells may be recovered providing that effective therapeutic interventions can be implemented at the onset of the disease. Once islet cell autoimmunity has begun, progression to islet cell destruction is quite variable, with some patients rapidly progressing to clinical diabetes while others remain in a nonprogressive state. Antigenic/epitope spreading of the autoantibody responses is an important marker of impending progression; those with but a single autoantibody progress slowly, whereas those with autoantibodies to multiple antigens most often progress rapidly. Most individuals progressing to overt diabetes express multiple anti-islet antibodies (GAD65, ICA512/IA-2, and IAA) by the time of diabetes onset. The autoimmune response against the pancreatic β cells is believed to consist of four phases: (1) environmental insult, (2) priming of T cells, (3) T-cell differentiation, and (4) β -cell destruction (Fig. 583–3).

Environment. Pathogens can initiate or precipitate the self-reactive process by three possible mechanisms. First, molecular mimicry between viral proteins and self-proteins expressed by β cells (i.e., PC2 protein of coxsackie virus and GAD65, rubella virus capsid protein and 52-kd islet protein, cytomegalovirus and 38-kd islet protein). Second, after acute β -cell infection or β -cell damage induced by cytokines during inflammatory responses against pathogens, the released proteins can be taken up by antigen presenting cells (APCs), which present the self-peptides to T cells. Third, cytokines secreted during a viral infection can upregulate the expression of co-stimulatory and MHC molecules on the surface of the facultative or nonfacultative APCs, enabling them to present self-peptides in immunogenic form to T cells. Exposure to microbial and viral pathogens early in life may also be protective against the development of type 1 DM.

Priming of T Cells. The presentation of β cell-specific autoantigens by APC macrophages or dendritic cells (DCs) to CD4 T helper (Th) cells in association with MHC class II molecules is considered the first step in the initiation of disease process (see

Fig. 583–3). Macrophages secrete interleukin (IL)-12, stimulating CD4 T cells to secrete interferon- γ and IL-2. Interferon- γ stimulates other resting macrophages to release, in turn, other cytokines such as IL-1 β , tumor necrosis factor (TNF)- α , and free radicals (NO, O $_2^-$), which are toxic to pancreatic β cells. During this process, cytokines induce the migration of β -cell autoantigen-specific CD8 cytotoxic cells. On recognizing specific autoantigens on β cells in association with class I molecule, these CD8 cytotoxic T cells cause β -cell damage by releasing perforin and granzyme and by Fas-mediated apoptosis of the β cells.

Differentiation of T Cells. Immune-mediated diabetes is associated with polyclonal populations of T cells reactive against multiple β -cell antigens. Thus T cells reactive against specific glutamic acid decarboxylase 65 (GAD65), proinsulin, tyrosine phosphatase (ICA512/IA-2), heat shock protein 60 (hsp60), and islet antigen 69 (ICA69) have been detected in type 1 DM patients. Among these antigens, GAD65 appears to be the early target of T cells. Because GAD65 is an intracellular protein, β -cell injury may be required to initiate the autoimmune process. The association between MHC class II and type 1 DM strongly suggests a pathogenic role of CD4 T cells, because MHC class II molecules are required for thymic education of precursors and for the restriction of CD4 T-cell responses. There is a correlation between the binding affinity of the peptide to MHC class II and antigenicity. Whereas the type 1 DM protective class II molecules bind self-peptides with high affinity and delete thymic precursors, type 1 DM-susceptible class II molecules bind self-peptides with low affinity, leading to a failure of central tolerance and escape of self-reactive T cells to periphery. T cells are differentiated into Th1 and Th2 effector cells. Th1 cells protect against intracellular microbes and parasites, and mediate delayed-type hypersensitivity and acute allograft rejection, whereas Th2 cells regulate humoral immune responses (IgE and IgG1), mediate allergic reactions, and protect against organ-specific autoimmune diseases such as type 1 DM, multiple sclerosis, thyroiditis, and Crohn disease. CD4 Th1 cells secrete IL-2 and interferon- γ and are associated with cell-mediated immunity. Th2 cells secrete IL-4 and IL-10, and are associated with humoral and anti-inflammatory responses. A subset of regulatory T cells known as natural killer T (NKT) cells prevents diabetes by secretion of IL-4 and/or IL-10. The regulatory Th3 (CD4) cells also tend to exert antidiabetogenic effect by the secretion of the suppressive cytokine tumor growth factor- β . Functional abnormalities in these regulatory cells may also play a role in the pathogenesis of type 1 DM.

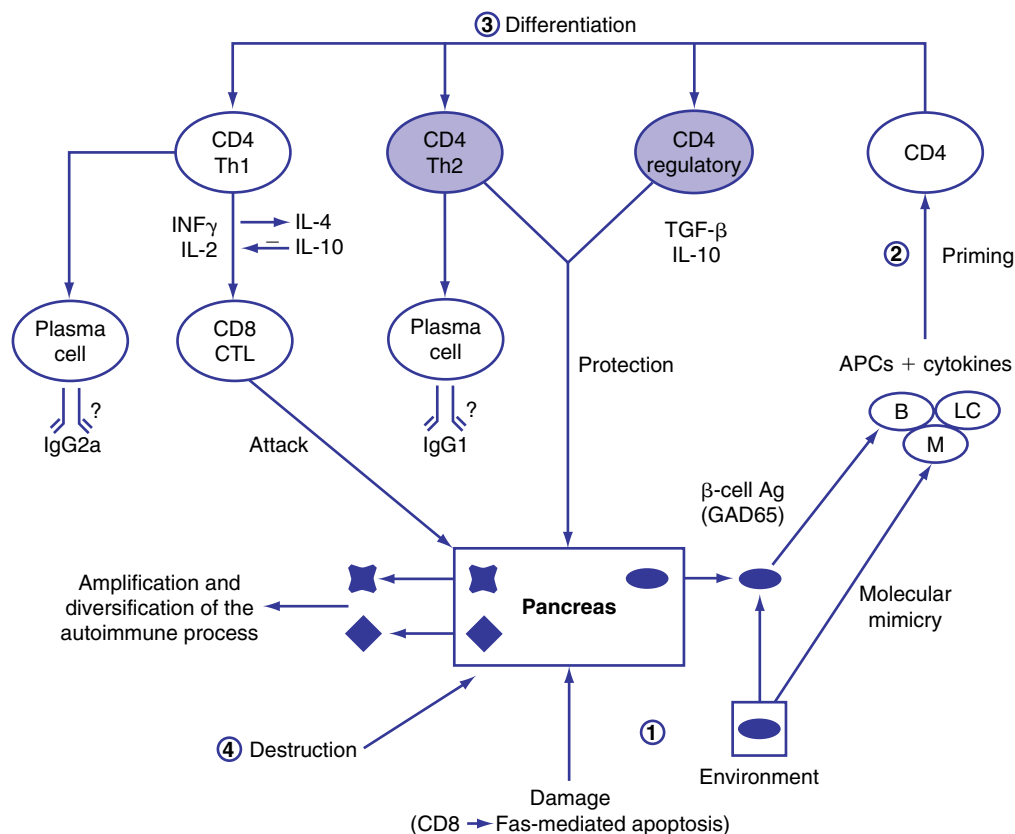


FIGURE 583-3. Schematic representation of the autoimmune response against the pancreatic β cells. An insult on the pancreas leads to the release of β -cell antigens (GAD65), which are taken up by antigen-presenting cells (APCs) and the epitopes presented to the CD4 T cells. Type and stages of activation of APCs as well as the cytokine environment, in which the CD4 T cell priming takes place, dictate the differentiation of autoreactive T cells toward diabetogenic T helper-1 (Th1) cells, Th2 cells, or antigen-specific regulatory T cells. A predominant Th1 autoimmune response results in the recruitment and differentiation of cytotoxic CD8 cells, which attack the pancreatic β cells, leading to a massive release of β -cell antigens, epitope spreading, and destruction of the pancreatic islets. B, B cell; DC, dendritic cell; M, macrophage; CTL, cytotoxic cell; TGF- β , tumor growth factor- β ; $\text{INF}\gamma$, interferon- γ ; IL, interleukin. (Adapted from Casares S, Brumeanu TD: Insights into the pathogenesis of type 1 diabetes: A hint for novel immunospecific therapies. *Curr Molec Med* 2001;1:357-78.)

β -Cell Destruction. Mononuclear cell infiltration into the pancreatic islets (insulinitis) and a reduction of insulin-producing β cells are recognized as key pathologic features of type 1 DM. Pancreatic biopsy samples obtained from prediabetic patients and from those with recent-onset type 1 DM have shown various degrees of reduction in β -cell volume in all patients, yet insulinitis could not be identified in about 50%. When insulinitis is detected, the infiltrate is composed of CD8 and CD4 T cells, B cells, and macrophages, with a predominance of CD8 T cells. Inflamed islet cells show hyperexpression of MHC class I molecules. The degree of insulinitis and hyperexpression of MHC class I molecules correlates with deteriorating glycemic control and GAD65 antibody levels. Fas is detected on β cells within inflamed cells, whereas islet-infiltrating mononuclear cells express Fas ligand. An interaction between Fas on β cells and Fas ligand on infiltrating cells might trigger selective apoptotic β -cell death in inflamed cells, leading to type 1 DM.

Prediction and Prevention. Autoimmunity precedes clinical type 1 DM, and indicators of maturing autoimmune responses may be useful markers for disease prediction. Individuals at risk for type 1 DM can be identified using a combination of genetic, immunologic, and metabolic markers. The most informative genetic locus, HLA class II, confers about half of the total genetic risk but has a low positive predictive value (PPV) when used in the general population. Autoantibodies provide a practical readout of β -cell autoimmunity, are easily sampled in venous blood, and have become the mainstay of type 1 DM prediction efforts. Initially described in terms of the islet cell antibody (ICA) immunofluorescence assay on pancreatic sections, autoantibod-

ies are described in terms of defined ICA target antigens, such as insulin (IAA), glutamic acid dehydrogenase (GAD65), and the tyrosine phosphatase homologue ICA512/IA-2.

Autoantibodies are useful for detecting developing type 1 DM in close relatives of diabetic patients whose risk for diabetes is about 3.5–5.0%. However, most cases are sporadic rather than familial, necessitating general population screening. This has been difficult, in part, because the observed autoantibody prevalence greatly exceeds the low disease prevalence in nonrelatives, leading to high false-positive rates. Single defined autoantibody (d-aab) positivity may result from persistent memory B cells in lymph nodes or bone marrow after brief transient insulinitis not resulting in clinical diabetes. It has been suggested that because different d-aab appear sequentially over time during prediabetes, the presence of multiple d-aab may mark more persistent insulinitis and greater diabetes risk. In the first-degree relatives of patients with type 1 DM, the number of positive d-aab can help estimate the risk of developing type 1 DM: low risk (single d-aab: PPV of 2–6%), moderate risk (2 d-aab: PPV of 21–40%), and high risk (>2 d-aab: PPV of 59%–80%) over a 5-yr period. In children carrying the type 1 DM highest-risk genotype (HLA-DQB1*0201-DQA1*05/DQB1*0302-DQA1*03), insulinitis is almost 10 times more frequent (PPV 21%) than in children with other genotypes (PPV 2.2%). On the other hand, in general populations of children, some studies have suggested a very low overall PPV for single d-aab (0–0.5%), whereas overall PPV for multiple (≥ 2) d-aab has been reported to be as high as 19–50% (high risk) over a 2–8 yr period.

There is no known agent capable of preventing type 1 DM. There are several obstacles to finding a plausible prevention

strategy. These include (1) ethical issues surrounding prediction, (2) treatment dilemma, (3) selection of populations at risk and treatment strategies, and (4) finding new preventive agents. The ability to predict future cases of type 1 DM, although a major benefit to knowledge about the natural history of this disease, in the absence of a preventing agent raises ethical considerations related to induction of stress, lifestyle changes, and potential effects on insurability.

A second challenge facing the diabetes prevention efforts is treatment dilemma. It is well recognized that the most effective interventions are those that are started early in the autoimmune process. However, the process of disease prediction, using immunologic, genetic, and metabolic markers, is most accurate in the period close to the onset of overt diabetes. Consequently, many health care providers and researchers are faced with ethical and clinical conflicts wherein the most effective forms of therapy might involve treatment of individuals in a period in which disease prediction is less accurate. Also, it has been very difficult to find safe and benign forms of therapy that can be used in individuals who may never develop type 1 DM.

Another obstacle is the selection of type of populations and appropriate therapeutic approaches. Attempts to prevent type 1 DM need to address therapy of high-risk population (relatives of type 1 DM patients with positive immune markers) versus the general population with low risk of developing diabetes. Whereas clinical trials in high-risk populations may be more efficient and cost-effective, the general population approach may be more important because about 85% of new cases of type 1 DM have no family history of the disease. In the general population, a safe and benign therapy capable of interrupting adverse immune events and environmental agents or alterations in lifestyle providing avoidance of disease risk factors would ideally be implemented. There is a considerable cost associated with screening general populations. Vitamin D supplementation of infants and maternal intake of cod liver oil during pregnancy have been shown to be associated with the reduced risk of type 1 DM in children. This protective effect of vitamin D is believed to be due to its immunosuppressive action, reducing lymphocyte proliferation and cytokine production. Therefore, age-appropriate vitamin D supplementation of all infants can be a relatively inexpensive strategy in the general population.

Another issue is the lack of an obvious therapeutic agent for diabetes prevention. For instance, the United States Diabetes Prevention Trial I (DPT-I) was started in 1994 to determine whether antigen-based therapies with insulin (i.e., low-dose parenteral insulin therapy to high-risk relatives or oral insulin vs placebo to intermediate-risk relatives) would prevent or delay the onset of diabetes. Therapy did not provide evidence for disease prevention, and the 2-yr results of oral insulin and low-dose parenteral insulin will be released soon.

IMMUNOTHERAPY IN NEW-ONSET TYPE 1 DM. Type 1 DM is a T-cell-mediated autoimmune disease that begins, in many cases, 3–5 yr before the onset of clinical symptoms, continues after diagnosis, and can recur after islet transplantation. The effector mechanisms responsible for the destruction of β -cells involve cytotoxic T cells as well as soluble T-cell products, such as interferon- γ and TNF- α . Such observations have led to clinical trials with immunomodulatory drugs such as cyclosporine, azathioprine, prednisone, and antithymocyte globulin, which were shown to cause transient improvement in clinical measures and to increase the rate of non-insulin-requiring remissions when initiated soon after diagnosis. Unfortunately, the toxic effects of such drugs, concern about the risk associated with immune suppression, and the need for continuous treatment in an otherwise healthy, young population limit the use of these agents.

Immunotherapy using modified monoclonal antibody against CD3 hOKT3 γ 1 has efficacy in patients with renal-allograft rejection. Treatment with hOKT3 γ 1 infusions mitigates the deteriora-

tion in insulin production and improves metabolic control during the 1st yr of type 1 DM in a majority of patients. The side effects include transient fever, gastrointestinal symptoms, and pruritic rash, without any long-term toxic effects up to 2 yr. The mechanisms of action of the anti-CD3 monoclonal antibody may involve direct effects on pathogenic T cells and/or the induction of populations of regulatory cells.

Pathophysiology. Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use. Insulin levels must be lowered to then mobilize stored energy during the fasted state. Thus, in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue (Table 583–3). Type 1 DM is a progressive low-insulin catabolic state in which feeding does not reverse but rather exaggerates these catabolic processes. With moderate insulinopenia, glucose utilization by muscle and fat decreases and postprandial hyperglycemia appears. At even lower insulin levels, the liver produces excessive glucose via glycogenolysis and gluconeogenesis, and fasting hyperglycemia begins. Hyperglycemia produces an osmotic diuresis (glucosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L). The resulting loss of calories and electrolytes, as well as the persistent dehydration, produce a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon). These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose utilization and glucose clearance (epinephrine, growth hormone, cortisol).

The combination of insulin deficiency and elevated plasma values of the counter-regulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids. The hormonal interplay of insulin deficiency and glucagon excess shunts the free fatty acids into ketone body formation; the rate of formation of these ketone bodies, principally β -hydroxybutyrate and acetoacetate, exceeds the capacity for peripheral utilization and renal excretion. Accumulation of these ketoacids results in

TABLE 583–3. Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue*

	High Plasma Insulin (Postprandial State)	Low Plasma Insulin (Fasted State)
Liver	Glucose uptake Glycogen synthesis Absence of gluconeogenesis Lipogenesis Absence of ketogenesis	Glucose production Glycogenolysis Gluconeogenesis Absence of lipogenesis Ketogenesis
Muscle	Glucose uptake Glucose oxidation Glycogen synthesis Protein synthesis	Absence of glucose uptake Fatty acid and ketone oxidation Glycogenolysis Proteolysis and amino acid release
Adipose tissue	Glucose uptake Lipid synthesis Triglyceride uptake	Absence of glucose uptake Lipolysis and fatty acid release Absence of triglyceride uptake

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, untreated, results in exaggerated fasting.

metabolic acidosis (diabetic ketoacidosis, DKA) and compensatory rapid deep breathing in an attempt to excrete excess CO₂ (Kussmaul respiration). Acetone, formed by nonenzymatic conversion of acetoacetate, is responsible for the characteristic fruity odor of the breath. Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte. With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

Clinical Manifestations. As diabetes develops, symptoms steadily increase, reflecting the decreasing β -cell mass, worsening insulinopenia, progressive hyperglycemia, and eventual ketoacidosis. Initially, when only insulin reserve is limited, occasional hyperglycemia occurs. When the serum glucose increases above the renal threshold, intermittent polyuria or nocturia begins. With further β -cell loss, chronic hyperglycemia causes a more persistent diuresis, often with nocturnal enuresis; polydipsia becomes more apparent. Female patients may develop monilial vaginitis due to the chronic glucosuria. Calories are lost in the urine (glucosuria), triggering a compensatory hyperphagia. If this hyperphagia does not keep pace with the glucosuria, loss of body fat ensues, with clinical weight loss and diminished subcutaneous fat stores. An average healthy 10-yr-old child consumes about 50% of 2,000 daily calories as carbohydrate. As that child becomes diabetic, daily losses of water and glucose may be 5 L and 250 g, respectively, representing 1,000 calories, or 50%, of the average daily caloric intake. Despite the child's compensatory increased intake of food, the body starves, because unused calories are lost in the urine.

When extremely low insulin levels are reached, ketoacids accumulate. At this point, the child quickly deteriorates. Ketoacids produce abdominal discomfort, nausea, and emesis, preventing oral replacement of urinary water losses. Dehydration accelerates, causing weakness or orthostasis—but polyuria persists. As in any hyperosmotic state, the degree of dehydration may be clinically underestimated because intravascular volume is conserved at the expense of intracellular volume. Ketoacidosis exacerbates prior symptoms and leads to Kussmaul respirations (deep heavy rapid breathing), fruity breath odor (acetone), diminished neurocognitive function, and possible coma. About 20–40% of children with new-onset diabetes progress to DKA before diagnosis.

This entire progression happens much more quickly (over a few weeks) in younger children, probably due to a more aggressive autoimmune destruction of β cells. In infants, most of the weight loss is acute water loss, because they will not have had a prolonged caloriuria when diagnosed, and there will be an increased incidence of DKA at diagnosis. In adolescents, the course is usually more prolonged (over months), and most of the weight loss represents fat loss due to prolonged starvation. Additional weight loss due to acute dehydration may occur just before diagnosis. In any child, the progression of symptoms may be accelerated by the stress of an intercurrent illness or trauma, when counter-regulatory (stress) hormones overwhelm the limited insulin secretory capacity.

Diagnosis. The diagnosis of type 1 diabetes is usually straightforward if considered in the differential diagnosis. Although most symptoms are nonspecific, the most important clue is an inappropriate polyuria in any child with dehydration, poor weight gain, or “the flu.” Hyperglycemia, glucosuria, and ketonuria can be determined quickly. Nonfasting blood glucose greater than 200 mg/dL (11.1 mmol/L) with typical symptoms is diagnostic with or without ketonuria. In the obese child, type 2 diabetes must be considered (see later text). Once hyperglycemia is confirmed, it is prudent to determine whether DKA is present (especially if ketonuria is found) and to evaluate electrolyte abnormalities—even if signs of dehydration are minimal.

A baseline glycohemoglobin (HbA_{1c}) allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy.

In the nonobese child, testing for autoimmunity to β cells is not necessary. Other autoimmunities associated with type 1 diabetes should be screened, including celiac disease (tissue transglutaminase IgA and total IgA) and thyroiditis (antithyroid peroxidase and antithyroglobulin antibodies). Because significant physiologic distress can disrupt the pituitary-thyroid axis, a free thyroxine (T₄) and TSH should be checked after the child is stable for a few weeks.

Rarely, a child has transient hyperglycemia with glucosuria while under substantial physical stress. This usually resolves permanently during recovery from the stressors. However, such stress hyperglycemia could reflect a limited insulin reserve temporarily revealed by counter-regulatory hormones. A child with temporary hyperglycemia should therefore be monitored for the development of symptoms of persistent hyperglycemia and tested if such symptoms occur. Formal testing in a child who remains clinically asymptomatic is not necessary.

Routine screening procedures, such as postprandial determinations of blood glucose or screening oral glucose tolerance tests, have yielded low detection rates in healthy, asymptomatic children, even among those considered at risk, such as siblings of diabetic children. Accordingly, such screening procedures are not recommended in children.

DIABETIC KETOACIDOSIS. DKA is the end result of the metabolic abnormalities resulting from a severe deficiency of insulin or insulin effectiveness. The latter occurs during stress as counter-regulatory hormones block insulin action. DKA occurs in 20–40% of children with new-onset diabetes, and in children with known diabetes who omit insulin doses or who do not successfully manage an intercurrent illness. DKA may be arbitrarily classified as mild, moderate, or severe (Table 583–4), and the range of symptoms depends on the depth of ketoacidosis. There is a large ketonuria, an increased ion gap, a decreased serum bicarbonate (or total CO₂) and pH, and an elevated effective serum osmolality indicating hypertonic dehydration.

Treatment. Therapy is tailored to the degree of insulinopenia at presentation. Most children with new diabetes (60–80%) have mild to moderate symptoms, minimal dehydration with no history of emesis, and have not progressed to ketoacidosis. Once DKA has resolved in the newly diagnosed child, therapy is transitioned to that described for children with nonketotic onset. Children with previously diagnosed diabetes who develop DKA are usually transitioned to their previous insulin regimen.

NEW ONSET DIABETES WITHOUT KETOACIDOSIS. Excellent diabetes control involves many goals: to maintain a balance between tight glucose control and avoiding hypoglycemia, to eliminate polyuria and nocturia, to prevent ketoacidosis, and to

TABLE 583–4. Classification of Diabetic Ketoacidosis

	Normal	Mild	Moderate	Severe [†]
CO ₂ (mEq/L, venous)*	20–28	16–20	10–15	<10
pH (venous)*	7.35–7.45	7.25–7.35	7.15–7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*CO₂ and pH measurement are method dependent; normal ranges may vary.

[†]Severe hypernatremia (corrected Na > 150 mEq/L) would also be classified as severe DKA.

permit normal growth and development with minimal effect on lifestyle. Therapy encompasses initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishing the routine of life. Each aspect should be addressed early in the overall care for the family. Ideally, therapy can begin in the outpatient setting, with complete team staffing by a pediatric endocrinologist, experienced nursing staff, dietitians with training as diabetes educators, and a social worker. Close contact between the diabetes team and family must be assured. Otherwise, initial therapy should be done in the hospital setting.

INSULIN. Several factors influence the initial daily insulin dose per kilogram of body weight. The dose is usually higher in pubertal children. It is higher in those who have to restore greater deficits of body glycogen, protein, and fat stores and who, therefore, have higher initial caloric capacity. On the other hand, most children with new-onset diabetes have some residual β -cell function (the “honeymoon” period), which reduces exogenous insulin needs. Children with longstanding diabetes and no insulin reserve require about 0.7 units/kg/d if prepubertal, 1.0 unit/kg/d at midpuberty, and 1.2 units/kg/d by the end of puberty. A reasonable dose in the newly diagnosed child, then, is about 60–70% of the full replacement dose based on pubertal status. The optimal insulin dose can only be determined empirically, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team. Residual β -cell function usually fades within a few months and is reflected as a steady increase in insulin requirements and wider glucose excursions.

The initial insulin *schedule* should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β cell. There are inherent limits to our ability to mimic the β cell. Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose; absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin release ceases and serum levels quickly lower with a normally rapid clearance; and absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation. Despite these fundamental physiologic differences, quite acceptable glucose control can be obtained with new insulin analogs used in a basal-bolus regimen, that is, with slow onset, long duration background insulin for between meal glucose control, and rapid-onset insulin at each meal.

All preanalog insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation. Thus, a detectable effect for regular (R) insulin is delayed by 30–60 min after injection. This, in turn, requires delaying the meal 30–60 min after the injection for optimal effect—a delay rarely attained in a busy child’s life. R has a wide peak and a long tail for bolus insulin (Figs. 583–4 and 583–5). This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia. These unwanted between-meal effects often necessitate “feeding the insulin” with snacks and limiting the overall degree of blood glucose control. NPH and Lente insulins also have inherent limits because they do not create a peakless background insulin level (see Fig. 583–4C–E). This produces significant hypoglycemic effect during the midrange of their duration. Thus, it is often difficult to predict their interaction with fast-acting insulins. When R is combined with NPH or lente (see Fig. 583–4E), the composite insulin profile poorly mimics normal endogenous insulin secretion. There are broad areas of excessive insulin effect alternating with insufficient effect throughout the day and night.

Lispro (L) and aspart (A), insulin analogs, are absorbed much quicker because they do not form hexamers. They provide discrete pulses with little if any overlap and short tail effect. This

allows better control of postmeal glucose increase and reduces between meal or nighttime hypoglycemia (Fig. 583–4A). The long-acting analog glargine (G) creates a much flatter 24-hr profile, making it easier to predict the combined effect of a rapid bolus (L or A) on top of the basal insulin, producing a more physiologic pattern of insulin effect (see Fig. 583–4A). Postprandial glucose elevations are better controlled, and between meal and nighttime hypoglycemia are reduced.

Ultralente (UL) given twice a day can provide a reasonable basal profile (see Fig. 583–5C) and is quite effective when used with lispro or aspart (see Fig. 583–4B). This combination may be used in children for whom glargine does not produce a complete 24-hr basal coverage.

The basal insulin glargine should be 25–30% of the total dose in toddlers and 40–50% in older children. The remaining portion of the total daily dose is divided evenly as bolus injections for the three meals. A simple three- or four-step dosing schedule is begun based on the blood glucose level (Table 583–5). As soon as the family is taught to calculate the carbohydrate content of meals, bolus insulin can be more accurately dosed by both the carbohydrate content of the meal as well as ambient glucose (see Table 583–5).

Frequent blood glucose monitoring and insulin adjustment are necessary in the first weeks as the child returns to routine activities and adapts to a new nutritional schedule, and as the total daily insulin requirements are determined. The major physiologic limit to tight control is hypoglycemia. Intensive control dramatically reduces the risk of long-term vascular complications; it is associated with a three-fold increase in severe hypoglycemia. Use of insulin analogs moderates but does not eliminate this problem.

Some families may be unable to administer four daily injections. In these cases, a compromise may be needed. A three-injection regimen combining the basal insulin ultralente (at breakfast and supper) with a rapid analog bolus at each meal may provide good glucose control. Further compromise to a two-injection regimen may occasionally be needed. This would require NPH or lente combined with a rapid analog bolus at breakfast and supper. However, such a schedule would provide poor coverage for lunch and early morning, and would increase the risk of hypoglycemia at midmorning and early night.

INSULIN PUMP THERAPY. Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared to conventional insulin injection regimens. Insulin pump therapy in adolescents with type 1 DM is associated with improved metabolic control and reduced risk of severe hypoglycemia without affecting psychosocial outcomes. The use of overnight CSII improves the metabolic control in children ages 7–10 yr. CSII has also been useful in toddlers. Others have demonstrated that CSII was associated with improved metabolic control in only 39% of patients and that the remainder of the patients either did not show reduction in HbA_{1c} (41%) or showed deterioration in metabolic control (20%). These investigators reported a mean HbA_{1c} of 8.3%, which is similar to that reported by the Diabetes Control and Complications Trial (DCCT) adolescents of 8.1%. The degree of glycemic control is mainly dependent on how closely patients adhere to the principles of diabetes self-care, regardless of the type of intensive insulin regimen. A greater proportion of patients on insulin pump therapy experience decreased seizure and hypoglycemic frequency as well as severe hypoglycemic episodes. CSII therapy is not associated with an abnormal increase in body weight.

INHALED AND ORAL INSULIN THERAPIES. Preprandial inhaled insulin is being evaluated in adults with type 1 and type 2 DM. The preliminary metabolic data is promising. Patients on premeal inhaled insulin in combination with once daily bedtime long-acting insulin (ultralente) injection achieved similar

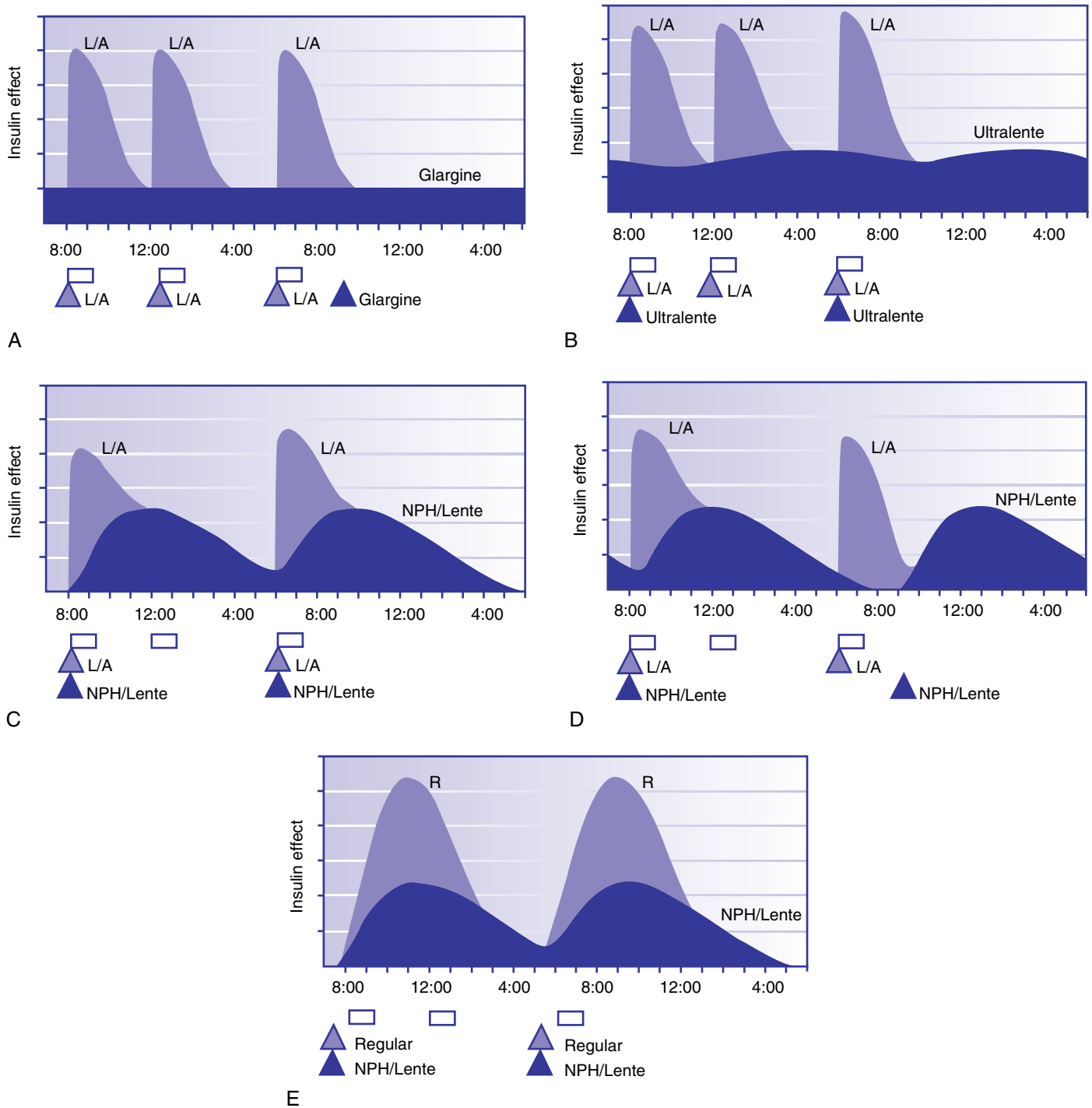


FIGURE 583-4. Approximate composite insulin effect profiles. Meals are shown as rectangles below time axis. Injections are shown as labeled triangles. L/A = lispro or aspart. Even though the fast and long-acting insulins are shaded differently to show the addition of one insulin effect to another, the profile is changed to show the combined effect. For example, in the breakfast injection in C, the quick decline of L/A effect is blunted by the rising NPH/lente effect, producing a broad tail, which slowly declines to baseline at supper. All profiles are idealized using average absorption and clearance rates. In typical clinical situations, these profiles vary among patients. A given patient has varying rates of absorption depending on the injection site, physical activity, and other variables. A, L or A pre-meal; glargine at bedtime. The rapid onset and short duration of L or A reduce overlap between pre-meal injections, and there is no extended nighttime action. This reduces the risk of hypoglycemia. Glargine provides a steady basal profile that simplifies prediction of bolus insulin effect. B, L or A pre-meal; ultralente at breakfast and supper. Ultralente produces a basal profile similar to that seen with glargine. Some excessive insulin effect, however, is seen before supper and at nighttime. C, L or A pre-meal; NPH or lente at breakfast and supper. The broad peak of NPH or lente produces substantial risk of hypoglycemia before lunch and during the early hours of the night. The waning insulin effect before supper and breakfast may also allow breakthrough hyperglycemia. D, L or A pre-meal; NPH or lente at breakfast and bedtime. Moving the evening long-acting insulin helps to cover the pre-breakfast hours, but the risk of nighttime lows persists. E, Regular and NPH or lente at breakfast and supper. This produces the least physiologic profile, with large excesses before lunch and during the early night, combined with poor coverage before supper and breakfast.

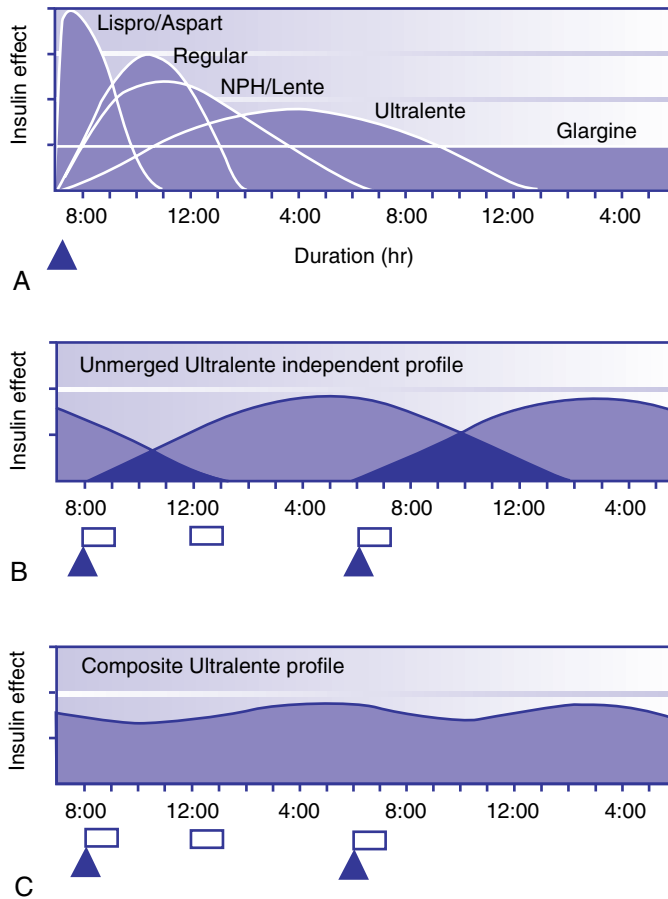


FIGURE 583-5. Approximate insulin effect profiles. *A*, The following relative peak effect and duration units are used: lispro/aspart, peak 20 for 4 hours; regular, peak 15 for 7 hours; NPH/lente, peak 12 for 12 hours; ultralente, peak 9 for 18 hours; glargine, peak 5 for 24 hours. ▲, Injection time. *B*, Two ultralente injections given at breakfast and supper. Note overlap of profiles. *C*, Composite curve showing approximate cumulative insulin effect for the two ultralente injections. This composite view is much more useful to the patient, parents, and medical personnel because it shows important combined effects of multiple insulin injections with variable absorption characteristics and overlapping durations.

metabolic control compared to patients on two to three daily injections of insulin. There was no significant difference in the frequency of hypoglycemic episodes between the two groups. There have been reports of pulmonary fibrosis in a small number of patients, necessitating further monitoring and evaluation of patients on inhaled insulin before this route of insulin administration is deemed safe.

Premeal oral insulin (Oralin) has been evaluated in comparison with oral hypoglycemic agents, mostly in patients with type 2 DM. The clinical data appears promising, but further evaluation of its efficacy in type 1 DM is needed.

BASIC EDUCATION. Therapy consists not only of initiation and adjustment of insulin dose but also of education of the patient and family. Teaching is most efficiently provided by experienced diabetes educators and nutritionists. In the acute phase, the family must learn the “basics,” which includes monitoring the child’s blood glucose and urine ketones, preparing and injecting the correct insulin dose subcutaneously at the proper time, recognizing and treating low blood glucose reactions, and having a basic meal plan. Most families trying to

adjust psychologically to the new diagnosis of diabetes in their child consequently have a limited ability to retain new information. Written materials covering these basic topics help the family during the first few days.

KETOACIDOSIS. Severe insulinopenia (or lack of effective insulin action) results in a physiologic cascade of events in three general pathways.

1. Excessive glucose production coupled with reduced glucose utilization raises serum glucose. This produces an osmotic diuresis, with loss of fluid and electrolytes, dehydration, and activation of the renin-angiotensin-aldosterone axis with accelerated potassium loss. If glucose elevation and dehydration are severe and persist for several hours, the risk of cerebral edema increases.

2. Increased catabolic processes result in cellular losses of sodium, potassium, and phosphate.

3. Increased release of free fatty acids from peripheral fat stores supplies substrate for hepatic ketoacid production. When ketoacids accumulate, buffer systems are depleted and a metabolic acidosis ensues. Therapy must address both the initiating event in this cascade (insulinopenia) and the subsequent physiologic disruptions.

Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema. Any protocol must be used with caution and close monitoring of the patient. Adjustments based on sound medical judgment may be necessary for any given level of DKA (Table 583-6).

HYPERGLYCEMIA AND DEHYDRATION. Insulin must be given at the beginning of therapy to accelerate movement of glucose into cells, to subdue hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver. However, an initial insulin bolus does not speed recovery and may increase the risk of hypokalemia and hypoglycemia. Therefore, insulin infusion is begun without a bolus at a rate of 0.1 unit/kg/h. This approximates maximal insulin output in normal subjects during an oral glucose tolerance test. Rehydration also lowers glucose levels by improving renal perfusion and enhancing renal excretion. The combination of these therapies usually causes a rapid initial decline in serum glucose levels. Once glucose goes below 180 mg/dL (10 mmol/L), the osmotic diuresis stops and rehydration accelerates without further increase in the infusion rate.

Repair of hyperglycemia occurs well before correction of acidosis. Therefore, insulin is still needed to control fatty acid release after normal glucose levels are reached. To continue the

TABLE 583-5. Subcutaneous Insulin Dosing

Age (years)	Target Glucose (mg/dL)	Total Daily Insulin (units/kg/d)*	Basal Insulin, % of Total Daily Dose	Bolus† Insulin	
				Units Added per 100 mg/dL above Target	Units Added Per 15 g at Meal
0-5	100-200	0.6-0.7	25-30	0.50	0.50
5-12	80-150	0.7-1.0	40-50	0.75	0.75
12-18	80-150	1.0-1.2	40-50	1.0-2.0‡	1.0-2.0

*Newly diagnosed children in the “honeymoon” may only need 60-70% of a full replacement dose. Total daily dose per kg increases with puberty.

†Newly diagnosed children who do not use carbohydrate dosing should divide the nonbasal portion of the daily insulin dose into equal doses for each meal. A dosing scale is then added for each dose. **For example:** a 6-yr-old child who weighs 20 kg needs about (0.7 units/kg/24 hr × 20 kg) = 14 units/24 hr with 7 units (50%) as basal and 7 units as total daily bolus. Give basal as glargine at hs. Give 2 units lispro or aspart before each meal if the blood glucose is within target; subtract 1 unit if below target; add 0.75 unit for each 100 mg/dL above target (round the dose to the nearest 0.5 unit).

‡For more finessed control, extra insulin may be added for 50-mg/dL increments.

TABLE 583–6. Diabetic Ketoacidosis Treatment Protocol

Time	Therapy	Comments
1st hour	10–20 mL/kg IV bolus 0.9% NaCl or LR Insulin drip at 0.05 to 0.10 u/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema.
2nd hour until DKA resolution	0.45% NaCl; plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar <250 mg/dL (14 mmol/L)	IV rate = $\frac{85 \text{ mL/kg} + \text{maintenance} - \text{bolus}}{23 \text{ hr}}$ If K <3 mEq/L, give 0.5 to 1.0 mEq/kg as oral K solution <i>OR</i> increase IV K to 80 mEq/L No emesis; CO ₂ ≥ 16 mEq/L; normal electrolytes
Variable	Oral intake with subcutaneous insulin	

Note that the initial IV bolus is considered part of the total fluid allowed in the first 24 hr and is subtracted before calculating the IV rate.

Maintenance (24 hr) = 100 mL/kg (for the 1st 10 kg) + 50 mL/kg (for the 2nd 10 kg) + 25 mL/kg (for all remaining kg)

Sample calculation for a 30-kg child:

1st hour = 300 mL IV bolus 0.9% NaCl or LR

$$2\text{nd and subsequent hours} = \frac{(85 \text{ mL} \times 30) + 1750 \text{ mL} - 300 \text{ mL}}{23 \text{ hr}} = \frac{175 \text{ mL}}{\text{hr}} \quad (0.45\% \text{ NaCl with } 20 \text{ mEq/L KPhos and } 20 \text{ mEq/L Kac})$$

NaCl, sodium chloride; LR, lactated Ringer solution; KPhos, potassium phosphate; KAc, potassium acetate; I/O, input and output (urine, emesis).

insulin infusion without causing hypoglycemia, glucose must be added to the infusion, usually as 5% solution. Glucose should be added when the serum glucose has decreased to about 250 mg/dL (14 mmol/L) so that there is sufficient time to adjust the infusion before the serum glucose falls further. The insulin infusion can also be lowered from the initial maximal rate once hyperglycemia has resolved.

Repair of fluid deficits must be tempered by the potential risk of cerebral edema. It is prudent to approach any child in any hyperosmotic state with cautious rehydration. The effective serum osmolality ($E_{\text{osm}} = 2 \times [\text{Na}_{\text{uncorrected}}] + [\text{glucose}]$) is an accurate index of tonicity of the body fluids, reflecting intracellular and extracellular hydration better than measured plasma osmolality. It is calculated with sodium and glucose in mmol/L. This value is usually elevated at the beginning of therapy and should steadily normalize. A rapid decline, or a slow decline to a subnormal range, may indicate an excess of free water entering the vascular space and an increasing risk of cerebral edema. Therefore, patients should not be allowed oral fluids until rehydration is well progressed and significant electrolyte shifts are no longer likely. Limited ice chips may be given as a minimal oral intake. All fluid intake and output should be closely monitored.

Calculation of fluid deficits using clinical signs is difficult in children with DKA because intravascular volume is better maintained in the hypertonic state. For any degree of tachycardia, delayed capillary refill, decreased skin temperature, or orthostatic blood pressure change, the child with DKA will be more dehydrated than the child with a normotonic fluid deficit. The protocol in Table 583–6 corrects a deficit of 85 mL/kg (8.5% dehydration) for all patients in the first 24 hr. Children with mild DKA rehydrate earlier and can be switched to oral intake, whereas those with severe DKA and a greater volume deficit require 30–36 hr with this protocol. This more gradual rehydration of the child with severe DKA is an inherent safety feature. The initial intravenous bolus (20 mL/kg of glucose-free isotonic sodium salt solution such as Ringer lactate or 0.9% sodium chloride) for all patients ensures a quick volume expansion and may be repeated if clinical improvement is not quickly seen. This bolus is given as isotonic saline because the patient is inevitably hypertonic, keeping most of the initial infusion in the intravascular space. Subsequent fluid is hypotonic to repair the free water deficit, to allow intracellular rehydration, and to allow a more appropriate replacement of ongoing hypotonic urine losses.

The initial serum sodium is usually normal or low because of the osmolar dilution of hyperglycemia and the effect of an elevated sodium-free lipid fraction. An estimate of the reconstituted, or “true,” serum sodium for any given glucose level above 100 mg/dL (5.6 mmol/L) is calculated as follows:

$$[\text{Na}^+] + \left[\frac{\text{Glucose} - 100}{100} \right] \times 1.6$$

where glucose is in mg/dL, or

$$[\text{Na}^+] + \left[\frac{\text{Glucose} - 5.6}{5.6} \right] \times 1.6$$

where glucose is in mmol/L.

One should expect the sodium to increase about 1.6 mmol/L for each 100 mg/dL decline in the glucose. The corrected sodium is usually normal or slightly elevated and indicates a moderate hypernatremic dehydration. If the corrected value is greater than 150 mmol/L, severe hypernatremic dehydration may be present and may require slower fluid replacement. The sodium should steadily increase with therapy. Declining sodium may indicate excessive free water accumulation and a risk of cerebral edema.

CATABOLIC LOSSES. Both the metabolic shift to a catabolic predominance and the acidosis move potassium and phosphate from the cell to the serum. The osmotic diuresis, the kaliuretic effect of the hyperaldosteronism, and the ketonuria then accelerate renal losses of potassium and phosphate. Sodium is also lost with the diuresis, but free water losses are greater than isotonic losses. With prolonged illness and severe DKA, total body losses can approach 10–13 mEq/kg of sodium, 5–6 mEq/kg of potassium, and 4–5 mEq/kg of phosphate. These losses continue for several hours during therapy until the catabolic state is reversed and the diuresis is controlled. For example, 50% of infused sodium may be lost in the urine during IV therapy. Even though the sodium deficit may be repaired within 24 hr, intracellular potassium and phosphate may not be completely restored for several days.

Although patients with DKA have a total body potassium deficit, the initial serum level is often normal or slightly elevated. This is due to the movement of potassium from the intracellular space to the serum, both as part of the ketoacid buffering process and as part of the catabolic shift. These effects are reversed with therapy and potassium returns to the cell. (Note that therapy for hyperkalemia uses insulin and glucose in the same manner, i.e., to promote the anabolic movement of potassium into the cell.) Improved hydration increases renal blood flow, allowing for increased excretion of potassium in the elevated aldosterone state. The net effect is often a dramatic decline in serum potassium levels, especially in severe DKA, and can precipitate changes in cardiac conductivity, flattening of T waves, prolongation of the QRS complex, and cause skeletal muscle weakness or an ileus. The risk of myocardial dysfunction is increased with shock and acidosis. Potassium levels must be closely followed and electrocardiographic monitoring continued until DKA is substantially resolved. If needed, the parenteral

potassium can be increased to 80 mEq/L or an oral supplement can be given if there is no emesis. Rarely, the IV insulin must be temporarily stopped.

It is unclear whether phosphate deficits contribute to symptoms of DKA such as generalized muscle weakness. In pediatric patients, a deficit has not been shown to compromise oxygen delivery via a deficiency of 2,3-diphosphoglycerate (2,3-DPG). Because the patient will receive an excess of chloride, which may aggravate acidosis, it is prudent to use potassium phosphate rather than potassium chloride as a potassium source. Potassium acetate is also used, because it provides an additional source of metabolic buffer.

Pancreatitis is occasionally seen with DKA, especially if prolonged abdominal distress is present; serum amylase may be elevated. If, however, the serum lipase is not elevated, the amylase is likely nonspecific or salivary in origin. Serum creatinine adjusted for age may be falsely elevated due to interference by ketones in the autoanalyzer methodology. An initial elevated value rarely indicates renal failure and should be rechecked when the child is less ketonemic. Blood urea nitrogen (BUN) may be elevated with prerenal azotemia and should be rechecked as the child is rehydrated. Mildly elevated creatine or BUN is not reason to withhold potassium therapy if good urinary output is present.

KETOACID ACCUMULATION. Low insulin infusion rates (0.02–0.05 units/kg/h) are sufficient to stop peripheral release of fatty acids, thus eliminating the flow of substrate for ketogenesis. Therefore, the initial infusion rate may be decreased if blood glucose levels go below 150 mg/dL (8 mmol/L) despite the addition of glucose to the infusion. Ketogenesis continues until fatty acid substrates already in the liver are depleted, but this production declines much more quickly without new substrate inflow. Bicarbonate buffers, regenerated by the distal renal tubule and by metabolism of ketone bodies, steadily repair the acidosis once ketoacid production is controlled. Bicarbonate therapy is rarely necessary and may even increase the risk of hypokalemia and cerebral edema.

There should be a steady increase in pH and serum bicarbonate as therapy progresses. Kussmaul respirations should abate and abdominal pain resolve. Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or, rarely, lactic acidosis. Urine ketones may be positive long after ketoacidosis has resolved because the nitroprusside reaction routinely used to measure urine ketones by dipstick only measures acetoacetate. During DKA, most excess ketones are β -hydroxybutyrate, which increases the normal ratio to acetoacetate from 3:1 to as high as 8:1. With resolution of the acidosis, β -hydroxybutyrate converts to acetoacetate, which is excreted into the urine and detected by the dipstick test. Therefore, persistent ketonuria may not accurately reflect the degree of clinical improvement and should not be relied upon as an indicator of therapeutic failure.

All patients with DKA should be checked for initiating events that triggered the metabolic decompensation, for example, an infection.

DKA PROTOCOL. (See Table 583–6.) Even though DKA can be of variable severity, a common approach to all cases simplifies the therapeutic regimen and can be safely used for most children. Fluids are best calculated based on weight, not body surface area (M^2), because heights are rarely available for the calculation. The Milwaukee protocol has been used for more than 20 yr in a large clinic setting with no deaths and no neurologic sequelae in any child treated with this protocol. It can be used for children of all ages and with all degrees of DKA. It is designed to restore most electrolyte deficits, to reverse the acidosis, and to rehydrate the moderately ill child in about 24 hr. A standard water deficit (85 mL/kg) is assumed. This amount, when added to maintenance, yields about 4 L/ M^2 for children of all sizes. Children with milder DKA recover in 10 to 20 hr (and

need less total IV fluid before switching to oral intake), whereas those with more severe DKA require 30 to 36 hr with this protocol. Any child can be easily transitioned to oral intake and subcutaneous insulin when DKA has essentially resolved (total $CO_2 > 15$ mEq/L; pH > 7.30 ; sodium stable between 135–145 mEq/L; no emesis). The IV is capped, and the first dose of subcutaneous insulin is given with a meal. Children with mild DKA can often be discharged after a few hours of therapy in the emergency department if adequate follow-up is provided.

A flow sheet is mandatory for accurate monitoring of changes in acidosis, electrolytes, fluid balance, and clinical status, especially if the patient is transferred from the emergency department to an inpatient setting with new caretakers. This flow sheet is best implemented by a central computer system, which allows for rapid update and wide availability of results, as well as rule-driven highlighting of critical values. A paper flow sheet suffices if it stays with the patient, is kept current, and is reviewed frequently by the physician. Any flow sheet should include columns for serial electrolytes, pH, glucose, and fluid balance. Blood testing should occur hourly for children with severe DKA and every 3–4 hr for those with mild to moderate DKA.

Even though this protocol has a long safety record, one must continue to *closely monitor each patient*. For all but the mildest cases, this should include frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, posturing, or seizures. Mannitol must be readily available for use at the earliest sign of cerebral edema. One must also keep informed of the laboratory changes; hypokalemia or hypoglycemia can occur rapidly. Children with moderate to severe DKA have a higher overall risk and should be treated in an intensive care environment. Finally, this protocol may not be appropriate for some patients such as the severely hypernatremic child (corrected sodium greater than 150 mEq/L) who may need slower rehydration with a longer duration of isotonic fluids.

Some residual β -cell function is seen even in children presenting with DKA. This function may improve as the child recovers from the effects of hyperglycemia and elevated counter-regulatory hormones. This residual secretion may necessitate a reduction in the initial total subcutaneous insulin dose used in the first few days of therapy.

NONKETOTIC HYPEROSMOLAR COMA. This syndrome is characterized by severe hyperglycemia (blood glucose greater than 800 mg/dL), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Respirations are usually shallow, but coexistent metabolic (lactic) acidosis may be manifested by Kussmaul breathing. Serum osmolarity is commonly 350 mOsm/kg or greater. This condition is uncommon in children; among adults, mortality rates have been as high as 40–70%, possibly in part because of delays in recognition and institution of appropriate therapy. In children, there has been a high incidence of pre-existing neurologic damage. Profound hyperglycemia may develop over a period of days and, initially, the obligatory osmotic polyuria and dehydration may be partially compensated for by increasing fluid intake. With progression of disease, thirst becomes impaired, possibly because of alteration of the hypothalamic thirst center by hyperosmolarity and, in some instances, because of a pre-existing defect in the hypothalamic osmoregulating mechanism.

The low production of ketones is attributed mainly to the hyperosmolarity, which in vitro blunts the lipolytic effect of epinephrine and the antilipolytic effect of residual insulin; blunting of lipolysis by the therapeutic use of β -adrenergic blockers may contribute to the syndrome. Depression of consciousness is

closely correlated with the degree of hyperosmolarity in this condition as well as in DKA; hemoconcentration may also predispose to cerebral arterial and venous thromboses.

Treatment of nonketotic hyperosmolar coma is directed at rapid repletion of the vascular volume deficit and very slow correction of the hyperosmolar state. One-half isotonic saline (0.45% NaCl; some use normal saline) is administered at a rate estimated to replace 50% of the volume deficit in the first 12 hr, and the remainder is administered during the ensuing 24 hr. The rate of infusion and the saline concentration are titrated to result in a slow decline of serum osmolality. When the blood glucose concentration approaches 300 mg/dL, the hydrating fluid should be changed to 5% dextrose in 0.2 normal (N) saline. Approximately 20 mEq/L of potassium chloride should be added to each of these fluids to prevent hypokalemia. Serum potassium and plasma glucose concentrations should be monitored at 2-hr intervals for the first 12 hr and at 4-hr intervals for the next 24 hr to permit appropriate adjustments of administered potassium and insulin.

Insulin can be given by continuous IV infusion beginning with the 2nd hr of fluid therapy. Blood glucose may decrease dramatically with fluid therapy alone. IV insulin dose should be 0.05 U/kg/h of regular (fast-acting) rather than 0.1 U/kg/h as advocated for patients with DKA.

NUTRITIONAL MANAGEMENT. Nutrition plays an essential role in the management of patients with type 1 DM. This is of critical importance during childhood and adolescence, when appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development. Nutritional treatment alone or in combination with appropriate insulin therapy averts or relieves symptoms of hyperglycemia in diabetic patients. Moreover, nutritional practices may influence the development of long-term complications of diabetes (i.e., diabetic nephropathy). There are no special nutritional requirements for the diabetic child other than those for optimal growth and development. In outlining nutritional requirements for the child on the basis of age, sex, weight, and activity, food preferences, including any based on cultural and ethnic backgrounds, must be considered.

Total recommended *caloric intake* is based on size or surface area and can be obtained from standard tables (Tables 583–7 and 583–8). The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein. Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited. Complex carbohydrates require prolonged digestion and absorption so that plasma glucose levels increase slowly, whereas glucose from refined sugars,

TABLE 583–8. Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus

Nutrition Care Plan

Promotes optimal compliance.

Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach.

Nutrient Recommendations and Distribution

Nutrient	(%) of Calories	Recommended Daily Intake
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber	>20 g per day	
Protein	12–20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6–8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000–4,000 mg if hypertensive

Additional Recommendations

Energy: If using measured diet, re-evaluate prescribed energy level at least every 3 mo.

Protein: High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore, 12–20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.

Alcohol: Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high.

Snacks: Snacks vary according to individual needs (generally three snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).

Alternative sweeteners: Use of a variety of sweeteners is suggested.

Educational techniques: No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.

Eating disorders: Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.

Exercise: Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.

From Connell JE, Thomas-Doberson D: *Nutritional management of children and adolescents with insulin-dependent diabetes mellitus: A review by the Diabetes Care and Education Dietetic Practice Group. J Am Diet Assoc 1991; 91:1556.*

including carbonated beverages, is rapidly absorbed and may cause wide swings in the metabolic pattern; carbonated beverages should be sugar-free. Priority should be given to total calories and total carbohydrate consumed rather than its source. *Carbohydrate counting* has become a mainstay in the nutrition education and management of patients with DM. Each carbohydrate exchange unit is 15 g. Patients and their families are provided with information regarding the carbohydrate contents of different foods and food label reading. This allows patients to adjust their insulin dosage to their mealtime carbohydrate intake. The use of carbohydrate counting and insulin to carbohydrate ratios and the use of fast-acting insulin analogs and long-acting basal insulins (ultralente and glargine) provide many children with less rigid meal planning. Flexibility in the use of insulin in relation to carbohydrate content of food improves the quality of life.

Although in children there is concern about the potential cumulative effect of saccharin, available data do not support an association of moderate amounts with bladder cancer. Other non-nutritive sweeteners such as aspartame are used in a variety of products. Sorbitol and xylitol should not be used as artificial sweeteners; they are products of the polyol pathway and are implicated in some of the complications of diabetes.

Diets with *high fiber content* are useful in improving control of blood glucose. Moderate amounts of sucrose consumed with fiber-rich foods such as whole meal bread may have no more glycemic effect than their low-fiber, sugar-free equivalents. The

TABLE 583–7. Calorie Needs for Children and Young Adults

Age	Kcal Required/Kg Body Weight*
Children	
0–12 mo	120
1–10 yr	100–75
Young women	
11–15 yr	35
≥16 yr	30
Young men	
11–15 yr	80–50 (65)
16–20 yr	
Average activity	40
Very physically active	50
Sedentary	30

Numbers in parentheses are means.

*Gradual decline in calories per unit weight as age increases.

From Nutrition Guide for Professionals: Diabetes Education and Meal Planning. Alexandria, VA, and Chicago, IL, The American Diabetes Association and The American Dietetic Association, 1988.

concept of biologic equivalence or of a “glycemic index” of foods is under investigation.

The *intake of fat* is adjusted so that the polyunsaturated:saturated ratio is increased to about 1.2:1.0, in contrast to the estimated American average of 0.3:1.0. Dietary fats derived from animal sources are, therefore, reduced and replaced by polyunsaturated fats from vegetable sources. Substituting margarine for butter, vegetable oil for animal oils in cooking, and lean cuts of meat, poultry, and fish for fatty meats, such as bacon, is advisable. The intake of cholesterol is also reduced by these measures and by limiting the number of egg yolks consumed. These simple measures reduce serum low-density lipoprotein cholesterol, a predisposing factor to atherosclerotic disease. Less than 10% of calories should be derived from saturated fats, up to 10% from polyunsaturated fats, and the remaining fat-derived calories from monounsaturated fats. Table 583–8 summarizes current nutritional guidelines.

The total daily caloric intake is divided to provide 20% at breakfast, 20% at lunch, and 30% at dinner, leaving 10% for each of the midmorning, midafternoon, and evening snacks, if they are desired. In older children, the midmorning snack may be omitted and its caloric equivalent added to lunch. Special brochures and pamphlets describing sample meal plans for children are usually available from regional diabetes associations; their use should be encouraged as part of the educational process. Meal plans are often based on groups of food exchanges; within each of the exchange lists of the foods that are principal sources of carbohydrates, proteins, and fats, there is a wide variety of foods that can be substituted or exchanged. There are few restrictions so that each child can select a diet based on personal taste or preferences with the help of the physician or dietitian, or both. Emphasis should be placed on regularity of food intake and on constancy of carbohydrate intake. Occasional excesses for birthdays and other parties are permissible and tolerated to not foster rebellion and stealth in obtaining desired food. Cakes and even candies are permissible on special occasions as long as the food exchange value and carbohydrate content are adjusted in the meal plan. Adjustments in meal planning must constantly be made to meet the needs as well as the desires of each child, although a consistent eating pattern with appropriate supplements for exercise, the pubertal growth spurt, and pregnancy in a diabetic adolescent are important for metabolic control. There is also an increased frequency of eating disorders among young women with diabetes. Thus, expectations and educational advice regarding nutrition must be dealt with in a sensitive careful manner, especially in adolescents.

MONITORING. Success in the daily management of the diabetic child can be measured by the competence acquired by the family, and subsequently by the child, in assuming responsibility for daily “diabetic care.” Their initial and ongoing instruction in conjunction with their supervised experience can lead to a sense of confidence in making intermittent adjustments in insulin dosage for dietary deviations, unusual physical activity, and even for some minor intercurrent illnesses, as well as for otherwise unexplained repeated hypoglycemic reactions and excessive glucosuria. Such acceptance of responsibility should make them relatively independent of the physician for their ordinary care. The physician must maintain ongoing interested supervision and shared responsibility with the family and the child.

Self-monitoring of blood glucose (SMBG) is an essential component of managing diabetes and necessitates a regimen that includes measurements of blood glucose and, at times, urinary ketones, as well as the keeping of a standardized record of these results and the corresponding data of dietary deviations, unusual physical activity, hypoglycemic reactions, intercurrent illness, the daily dose of insulin, and other items of possible relevance. When the physician mistrusts the patient’s record, physicians may make their own evaluations. If these data are counter

to those in the parent or child’s report, the physician can then attempt to clarify the situation in a manner that does not undermine their mutual confidence.

Daily blood glucose monitoring has been markedly enhanced by the availability of strips impregnated with glucose oxidase that permit blood glucose measurement from a drop of blood. A portable calibrated reflectance meter can approximate the blood glucose concentration accurately. Many meters contain a memory “chip” enabling recall of each measurement, its average over a given interval, and the ability to display the pattern on a computer screen. Such information is a useful educational tool for verifying degree of control and modifying recommended regimens. A small spring-loaded device that automates capillary blood letting (lancing device) in a relatively painless fashion is commercially available. Parents and patients should be taught to use these devices and measure blood glucose three to four times daily—before breakfast, lunch, and supper, and at bedtime. Initially, at diagnosis, the blood glucose measurement should also be performed at 12 AM and 3 AM to exclude inappropriate nocturnal hypoglycemia and avoid the Somogyi phenomenon. Ideally, the blood glucose concentration should range from approximately 80 mg/dL in the fasting state to 140 mg/dL after meals. In practice, however, a range of 60–220 mg/dL is acceptable, based on age of the patient. Blood glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose. If the fasting blood glucose is high, the evening dose of long-acting insulin is increased by 10–15% and/or the insulin (lispro or aspart) coverage for bedtime snack may be considered; if the noon glucose level exceeds set limits, the morning fast-acting insulin (lispro or aspart) is increased by 10–15%; if the presupper glucose is high, the noon dose fast-acting insulin is increased by 10–15%; and if the prebedtime glucose measurement is high, the presupper dose of fast-acting insulin is increased by 10–15%. Similarly, reductions in the insulin type and dose should be made if the corresponding blood glucose measurements are consistently below desirable limits.

A minimum of four daily blood glucose measurements should be performed. However, some children and adolescents may need to have more frequent blood glucose monitoring based on their level of physical activity and history of frequent hypoglycemic reactions. Families should be encouraged to become sufficiently knowledgeable about managing their diabetes. They can maintain near-normal glycemia for prolonged periods of time by self-monitoring of blood glucose levels before and 2 hr after meals, and in conjunction with multiple daily injections of insulin, adjusted as necessary, can maintain near-normal glycemia for prolonged periods.

The *continuous glucose monitoring system (CGMS)* records data obtained from a subcutaneous sensor every 5 min for up to 72 hr and provides the clinician with a continuous profile of tissue glucose levels. The interstitial glucose levels lag 13 min behind the blood glucose values independent of level in ambient blood glucose. The CGMS values tend to have high correlation coefficient for blood glucose values ranging between 40 and 400 mg/dL. CGMS is minimally invasive and entails the placement of a small, subcutaneous catheter that can be easily worn by adults and children. The system provides information that allows the patient and healthcare team to adjust the insulin regimen and the nutrition plan to improve glycemic control. CGMS can be helpful in detecting asymptomatic nocturnal hypoglycemia as well as in lowering HbA_{1c} values without increasing the risk for severe hypoglycemia. While there are potential pitfalls in CGMS use including suboptimal compliance, human error, incorrect technique and sensor failure, the implementation of CGMS in ambulatory diabetes practice allows the clinician to diagnose abnormal glycemic patterns in a more precise manner.

Glucowatch Biographer uses reverse iontophoresis to analyze the glucose content of interstitial fluid, which is extracted through a membrane patch on the patient's wrist beneath the Glucowatch device. Glucowatch provides realtime interstitial fluid glucose values, in the range of 40–400 mg/dL, that are the average of blood glucose values for the preceding 20 min. Glucose values in the range of 70–280 mg/dL have the highest correlation coefficient with blood glucose values. Additionally, Glucowatch alarm can be set for monitoring nocturnal hypoglycemia as needed.

A reliable index of long-term glycemic control is provided by measurement of *glycosylated hemoglobin*. HbA_{1c} represents the fraction of hemoglobin to which glucose has been nonenzymatically attached in the bloodstream. The formation of HbA_{1c} is a slow reaction that is dependent on the prevailing concentration of blood glucose; it continues irreversibly throughout the red blood cell's life span of approximately 120 days. The higher the blood glucose concentration and the longer the red blood cell's exposure to it, the higher is the fraction of HbA_{1c}, which is expressed as a percentage of total hemoglobin. Because a blood sample at any given time contains a mixture of red blood cells of varying ages, exposed for varying times to varying blood glucose concentrations, an HbA_{1c} measurement reflects the average blood glucose concentration of the preceding 2–3 mo. When measured by standardized methods to remove labile forms, the fraction of HbA_{1c} is not influenced by an isolated episode of hyperglycemia. Consequently, as an index of long-term glycemic control, a measurement of HbA_{1c} is superior to measurements of glycosuria or a single blood glucose determination. It is recommended that HbA_{1c} measurements be obtained three to four times per year to obtain a profile of long-term glycemic control. The more consistently lower the HbA_{1c} level, and hence the better the metabolic control, the more likely it is that microvascular complications such as retinopathy and nephropathy will be less severe, delayed in appearance, or avoided. Depending on the method used for determination, HbA_{1c} values may be spuriously elevated in thalassemia (or other conditions with elevated hemoglobin F) and spuriously lower in sickle cell disease. Although values of HbA_{1c} may vary according to the method used for measurement, in nondiabetic individuals, the HbA_{1c} fraction is usually less than 6%; in diabetics, values of 6–8.5% represent good metabolic control, values of 9–10%, fair control, and values of 11% or higher, poor control (Table 583–9).

EXERCISE. No form of exercise, including competitive sports, should be forbidden to the diabetic child. A major complication of exercise in diabetic patients is the presence of a hypoglycemic reaction during or within hours after exercise. If hypoglycemia does not occur with exercise, adjustments in diet or insulin are not necessary, and gluoregulation is likely to be improved through the increased utilization of glucose by muscles. The major contributing factor to hypoglycemia with exercise is an increased rate of absorption of insulin from its injection site.

Higher insulin levels dampen hepatic glucose production so that it is inadequate to meet the increased glucose utilization of exercising muscle. Regular exercise also improves gluoregulation by increasing insulin receptors. In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counter-regulatory hormones.

In anticipation of vigorous exercise, one additional carbohydrate exchange may be taken before exercise, and glucose from orange juice, carbonated nondietetic beverage, or candy should be available during and after exercise. With experience and trial and error, each patient, guided by the physician, should develop an appropriate regimen for regularly planned exercise that is frequently associated with hypoglycemia; in such instances, the total dose of insulin may be reduced by about 10–15% on the day of the scheduled exercise. Prolonged exercise, such as long-distance running may require reduction of as much as 50% or more of the usual insulin dose.

BENEFITS OF IMPROVED GLYCEMIC CONTROL. The DCCT established conclusively the association between higher glucose levels and long-term microvascular complications. Intensive management produced dramatic reductions of retinopathy, nephropathy, and neuropathy by 47–76%. The data from the adolescent cohort demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications. Adolescents gained more weight and experienced significantly more frequent episodes of severe hypoglycemia and ketoacidosis than did adults. Other studies of children and adolescents have not documented increased frequency or severity of hypoglycemia.

The beneficial effect of intensified treatment was determined by the degree of blood glucose normalization, independent of the type of intensified treatment used. Frequent blood glucose monitoring was considered an important factor in achieving better glycemic control for the intensively treated adolescents and adults. Patients who were intensively treated had individualized glucose targets, frequent adjustments based on ongoing capillary blood glucose monitoring, and a team approach that focused on the person with diabetes as the prime initiator of ambulatory care. Care was constantly adjusted toward reaching normal or near normal glycemic goals, while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a proactive (preventive) approach to blood glucose fluctuations with constant readjustment (reactive approach) to counterbalance any high or low blood glucose readings. Target blood glucose goals were adjusted upward if hypoglycemia could not be prevented.

Total duration of diabetes contributes to development and severity of complications. Nonetheless, many professionals have concerns about applying the results of the DCCT to preschool-aged children, who often have hypoglycemia unawareness with unique safety issues and to prepubertal school-aged children, who were not included in the DCCT.

CURRENT INTENSIVE INSULIN REPLACEMENT REGIMENS. The goal of physiologic insulin replacement for type 1 DM is accomplished with short-acting insulins that more closely mimic the sharp increase and short duration of pancreatic insulin secreted with nutrient intake. The rapid-acting insulin analog lispro has superior pharmacokinetic properties for the control of postprandial glucose. Improved postprandial glucose responses occur when treated with twice-daily injections (conventional insulin, CI), multiple daily injections (MDI), or CSII. The use of lispro or aspart insulin reduces the frequency of between-meal hypoglycemic events, especially when it is carefully balanced with the carbohydrate content of meal. This has improved how insulin is given to toddlers as well as when a flexible meal plan is desired.

The carbohydrate content of food does not influence glycemic control if premeal rapid-acting insulin (bolus) is adjusted to the

TABLE 583–9. Target Premeal and 30-Day Average Blood Glucose Ranges and the Corresponding Hemoglobin A_{1c} for each Age Group

Age Group (yr)	Target Premeal BG Range (mg/dL)	30-Day Average BG Range (mg/dL)	Target HbA _{1c} (%)
<5	100–200	180–250	7.5–9.0
5 to 11	80–150	150–200	6.5–8.0
12 to 15	80–130	120–180	6.0–7.5
16 to 18	70–120	100–150	5.5–7.0

In our laboratory the nondiabetic reference range for HbA_{1c} is 4.5–5.7% (95% confidence interval).

BG, blood glucose; HbA_{1c}, hemoglobin A_{1c}.

carbohydrate content of meal. Wide variations in carbohydrate intake do not modify long-acting (ultralente/glargine) or basal insulin requirement. Insulin replacement strategies stress the importance of administering smaller doses of insulin throughout the day. This approach allows insulin doses to be changed as needed to correct hyperglycemia, supplement for additional anticipated carbohydrate intake, or subtract for exercise. Indeed, bolus-basal treatment with multiple injections is better adapted to the physiologic profiles of insulin and glucose and can therefore provide better glycemic control than the conventional two- to three-dose regimen. Age-adjusted and individualized insulin to carbohydrate ratios and insulin dosage adjustment algorithms have been developed to normalize elevated blood glucose levels and to compensate for alterations in carbohydrate intake. The use of flexible multiple daily injections (FMDIs) and CSII in children with type 1 DM improves glycemic control without an increase in the incidence of severe hypoglycemia.

HYPOGLYCEMIC REACTIONS. Hypoglycemia is the major limitation to tight control of glucose levels. Once injected, insulin absorption and action are independent of the glucose level, thus creating a unique risk of hypoglycemia from an unbalanced insulin effect. Insulin analogs may help reduce but cannot eliminate this risk. Most children with type 1 diabetes can expect mild hypoglycemia each week, moderate hypoglycemia a few times each year, and severe hypoglycemia every few years. These episodes are usually not predictable, although exercise, delayed meals or snacks, and wide swings in glucose levels increase the risk. Infants and toddlers are at higher risk because they have more variable meals and activity levels, are unable to recognize early signs of hypoglycemia, and are limited in their ability to seek a source of oral glucose to reverse the hypoglycemia. The very young have an increased risk of permanently reduced cognitive function as a long-term sequela of severe hypoglycemia. For this reason, a more relaxed degree of glucose control is necessary until the child matures (see Table 583-9).

Hypoglycemia can occur at any time of day or night. Early symptoms and signs (mild hypoglycemia) may occur with a sudden decrease in blood glucose to levels that do not meet standard criteria for hypoglycemia in nondiabetic children (see Chapter 81). The child may show pallor, sweating, apprehension or fussiness, hunger, tremor, and tachycardia, all due to the surge in catecholamines as the body attempts to counter the excessive insulin effect. Behavioral changes such as tearfulness, irritability, aggression, and naughtiness are more prevalent in children. As glucose levels decline further, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, impaired judgment (moderate hypoglycemia), progressing to an inability to seek help, and seizures or coma (severe hypoglycemia). Prolonged severe hypoglycemia can result in a depressed sensorium or strokelike focal motor deficits that persist after the hypoglycemia has resolved. Although permanent sequelae are rare, severe hypoglycemia is frightening for the child and family, and can result in a significant reluctance to attempt even moderate glycemic control afterward.

Important counter-regulatory hormones in children include growth hormone, cortisol, epinephrine, and glucagon. The latter two seem more critical in the older child. Many older patients with long-standing type 1 diabetes lose their ability to secrete glucagon in response to hypoglycemia. In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy. This substantially increases the risk of hypoglycemia because the early warning signals of a declining glucose level are due to catecholamine release. Recurrent hypoglycemic episodes associated with tight metabolic control may aggravate partial counter-regulatory deficiencies, producing a syndrome of *hypoglycemia unawareness* and reduced ability to restore euglycemia (hypoglycemia-associated autonomic fail-

ure). Avoidance of hypoglycemia allows some recovery from this unawareness syndrome.

The most important factors in the management of hypoglycemia are an understanding by the patient and family of the symptoms and signs of the reaction and an anticipation of known precipitating factors such as gym or sports activities. Tighter glucose control increases the risk. Families should be taught to look for typical hypoglycemic scenarios or patterns in the home blood glucose log, so that they may adjust the insulin dose and avert predictable episodes. A source of emergency glucose should be available at all times and places, including at school and during visits to friends. If possible, it is initially important to document the hypoglycemia before treating, because some symptoms may not always be due to hypoglycemia. Most families and children develop a good sense for true hypoglycemic episodes and can institute treatment before testing. Any child suspected of having a moderate to severe hypoglycemic episode should also be treated before testing. It is important not to give too much glucose; 5–10 g should be given as juice or a sugar-containing carbonated beverage or candy and the blood glucose checked 15–20 minutes later. Patients, parents, and teachers should also be instructed in the administration of *glucagon* when the child cannot take glucose orally. An injection kit should be kept at home and school. The intramuscular dose is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg. This produces a brief release of glucose from the liver. Glucagon often causes emesis, which precludes giving oral supplementation if the blood glucose declines after the glucagon effect has waned. Caretakers must then be prepared to take the child to the hospital for IV glucose administration, if necessary.

THE SOMOGYI PHENOMENON, THE DAWN PHENOMENON, AND BRITTLE DIABETES. There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common is a simple decline in insulin levels and is seen in many children using NPH or lente as the basal insulin at supper or bedtime. This usually results in routinely elevated morning glucose. The *dawn phenomenon* is thought to be due mainly to overnight growth hormone secretion and increased insulin clearance. It is a normal physiologic process seen in most nondiabetic adolescents, who compensate with more insulin output. A child with type 1 diabetes cannot compensate and may actually have declining insulin levels if using evening NPH or lente. The dawn phenomenon is usually recurrent and modestly elevates most morning glucose levels.

Rarely, high morning glucose is due to the Somogyi phenomenon, a theoretical rebound from late night or early morning hypoglycemia, thought to be due to an exaggerated counter-regulatory response. It is unlikely to be a common cause, in that most children remain hypoglycemic once nighttime glucose levels decline. Continuous glucose monitoring systems should allow clarification of ambiguously elevated morning glucose levels.

The term *brittle diabetes* has been used to describe the child, usually an adolescent female, with unexplained wide fluctuations in blood glucose, often with recurrent DKA, who is on large doses of insulin. An inherent physiologic abnormality is rarely present because these children usually show normal insulin responsiveness when in the hospital environment. Psychosocial or psychiatric problems, including eating disorders, and dysfunctional family dynamics are usually present, which preclude effective diabetes therapy. Hospitalization is usually needed to confirm the environmental effect, and aggressive psychosocial or psychiatric evaluation is essential.

BEHAVIORAL/PsYCHOLOGICAL ASPECTS AND EATING DISORDERS. Diabetes in a child affects the lifestyle and interpersonal relationships of the entire family. Feelings of anxiety and guilt are common in parents. Similar feelings, coupled with denial and rejection, are equally common in children,

particularly during the rebellious teenage years. Family conflict has been associated with poor treatment adherence and poor metabolic control among youths with type 1 DM. No specific personality disorder or psychopathology is characteristic of diabetes; similar feelings are observed in families with other chronic disorders.

Nonadherence. Family conflict, denial, and feelings of anxiety find expression in nonadherence to instructions regarding nutritional and insulin therapy and in noncompliance with self-monitoring. Deliberate overdosage with insulin, resulting in hypoglycemia, or omission of insulin, often in association with excesses in nutritional intake and resulting in ketoacidosis, may be pleas for psychological help or manipulative attempts to escape an environment perceived as undesirable or intolerable; occasionally, they may be manifestations of suicidal intent. Frequent admissions to the hospital for ketoacidosis or hypoglycemia should arouse suspicion of an underlying emotional conflict. Overprotection on the part of parents is common and often is not in the best interest of the patient. Feelings of being different or of being alone, or both, are common and may be justified in view of the restrictive schedules imposed by testing of urine and blood, administration of insulin, and nutritional limitations. Furthermore, concern about the likelihood of complications developing and the decreased life span of patients with diabetes fosters anxiety. Unfortunately, misinformation abounds about the risks of the development of diabetes in siblings or offspring and of pregnancy in young diabetic women. Even appropriate information often causes further anxiety.

Many of these problems can be averted through continued empathic counseling based on correct information and attempts to build attitudes of normality in the patient and a feeling of being a productive member of society. Recognizing the potential impact of these problems, peer discussion groups have been organized in many locales; feelings of isolation and frustration tend to be lessened by the sharing of common problems. Summer camps for diabetic children afford an excellent opportunity for learning and sharing under expert supervision. Education about the pathophysiology of diabetes, insulin dose, technique of administration, nutrition, exercise, and hypoglycemic reactions can be reinforced by medical and paramedical personnel. The presence of numerous peers with similar problems offers new insights to the diabetic child. Residential treatment for children and adolescents with difficult to manage type 1 DM is an option available only in some centers.

Anxiety and Depression. It has been shown that there are significant correlations between a poor metabolic control and depressive symptoms, a high level of anxiety, or a previous psychiatric diagnosis. In a similar way, poor metabolic control is related to higher levels of personal, social, school maladjustment, or family environment dissatisfaction. It is estimated that between 20–26% of adolescent patients may develop major depressive disorder (MDD), which is similar to the occurrence rate of MDD in nondiabetic adolescents. The course characteristics of MDD in young diabetic subjects and psychiatric control subjects appear to be similar; however, eventual propensity of diabetic youths for more protracted depressions is greater and there is higher risk of recurrence among young diabetic females. Therefore, the health care providers managing a child or adolescent with diabetes should be aware of their pivotal role as counselor and advisor and should closely monitor the mental health of patients with diabetes.

Fear of Self-injecting and Self-testing. Extreme fear of self-injecting (FSI) insulin (injection phobia) is likely to compromise glycemic control as well as emotional well-being. Likewise, fear of finger pricks can be a source of distress and may seriously hamper self-management. Children and adolescents with FSI either omit insulin dosing and/or refuse to rotate their injection sites because repeated injections in the same site is associated with less pain sensation. Failure to rotate injection sites results

in subcutaneous scar formation (lipohypertrophy). Insulin injection into the lipohypertrophic skin is usually associated with poor insulin absorption and/or insulin leakage with resultant suboptimal glycemic control.

Eating Disorders. Treatment of type 1 DM involves constant monitoring of food intake. In addition, improved glycemic control is commonly associated with increased weight gain. In adolescent females, these two factors, along with individual, familial, and socioeconomic factors, can lead to an increased incidence of both nonspecific and specific eating disorders, which can disrupt glycemic control and increase the risk of long-term complications. Eating disorders and subthreshold eating disorders are almost twice as common in adolescent females with type 1 DM as in their nondiabetic peers. The reports of the frequencies of specific (anorexia or bulimia nervosa) eating disorders vary between 1–6.9% among female patients with type 1 DM. The prevalence of nonspecific and subthreshold eating disorders is 9% and 14%, respectively. About 11% of type 1 DM adolescent females take less insulin than prescribed to lose weight. Among adolescent females with an eating disorder, about 42% of patients misuse insulin, whereas the estimates of insulin misuse prevalence in subthreshold and nondisordered eating groups are 18% and 6%, respectively. While there is little information regarding the prevalence of eating disorders among male adolescents with type 1 DM, available data suggest normal eating attitudes in this group of patients. Among healthy adolescent males who participate in wrestling, however, the drive to lose weight has led to the seasonal, transient development of abnormal eating attitudes and behaviors, which may lead to insulin dose omission in order to lose weight.

When behavioral/psychological problems and/or eating disorders are assumed to be responsible for poor compliance with the medical regimen, referral for psychological evaluation and management is indicated. Children and adolescents with injection phobia and fear of self-testing can be counseled by a trained behavioral therapist and benefit from such techniques as desensitization and biofeedback to attenuate pain sensation and psychological distress associated these procedures. Behavioral therapists and psychologists usually form part of the pediatric diabetes team in most centers, and can help assess and manage emotional and behavioral disorders in diabetic children.

MANAGEMENT DURING INFECTIONS. While infections are no more common in diabetic children than in nondiabetic ones, they can often disrupt glucose control and may precipitate DKA. In addition, the diabetic child is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counter-regulatory hormones associated with stress blunt insulin action and elevate glucose levels. If anorexia occurs, however, lack of caloric intake increases the risk of hypoglycemia. Although children younger than 3 yr tend to become hypoglycemic and older children tend toward hyperglycemia, the overall effect is unpredictable. Therefore, frequent blood glucose monitoring and adjustment of insulin doses are essential elements of sick day guidelines (Table 583–10).

The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis. This can usually be done at home if proper sick day guidelines are followed and with telephone contact with health care providers. The family should seek advice if home treatment does not control ketonuria, hyperglycemia, or hypoglycemia, or if the child shows signs of dehydration. A child with large ketonuria and emesis should be seen in the emergency department for a general examination, to evaluate hydration, and to determine whether ketoacidosis is present by checking serum electrolytes, glucose, pH, and total CO₂. A child whose blood glucose declines to less than 50–60 mg/dL (2.8–3.3 mmol/L) and who cannot maintain oral intake may need IV glucose, especially if further insulin is needed to control ketonemia.

TABLE 583–10. Guidelines for Sick Day Management

Urine Ketone Status	Glucose Testing and Extra Insulin	Rapid-Acting Insulin Correction Doses*	Comments
Neg or small [†]	q2 hr	q2 hr for glucose > 250 mg/dL	Check ketones every other void.
Moderate to large [‡]	q1 hr	q1 hr for glucose > 250 mg/dL	Check ketones each void. Go to hospital if emesis occurs.

Basal insulin: glargine or ultralente basal insulin should be given at the usual dose and time. NPH and lente should be reduced by one half if blood glucose < 150 mg/dL and the oral intake is limited.

Oral fluids: sugar free if blood glucose > 250 mg/dL (14 mmol/L); sugar-containing if blood glucose < 250 mg/dL.

Call physician or nurse if blood glucose remains elevated after three extra doses; if blood glucose remains less than 70 mg/dL and child cannot take oral supplement; if dehydration occurs.

*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose > 150 mg/dL.

[†]For home serum ketones < 1.5 mmol/L per commercial kit.

[‡]For home serum ketones > 1.5 mmol/L.

MANAGEMENT DURING SURGERY. Surgery can disrupt glucose control in the same way as can intercurrent infections. Stress hormones associated with the underlying condition as well as with surgery itself decrease insulin sensitivity. This increases glucose levels, exacerbates fluid losses, and may initiate DKA. On the other hand, caloric intake is usually restricted, which decreases glucose levels. The net effect is as difficult to predict as during an infection. Vigilant monitoring and frequent insulin adjustments are required to maintain euglycemia and avoid ketosis.

Maintaining glucose control and avoiding DKA are best accomplished with IV insulin and fluids. A simple insulin adjustment scale based on the patient's weight and blood glucose level can be used in most situations (Table 583–11). The IV insulin is continued after surgery as the child begins to take oral fluids; the IV fluids can be steadily decreased as oral intake increases. When full oral intake is achieved, the IV may be capped and subcutaneous insulin begun. When surgery is elective, it is best performed early in the day, allowing the patient maximal recovery time to restart oral intake and subcutaneous insulin therapy. When elective surgery is brief (less than 1 hr) and full oral intake is expected shortly afterward, one may simply monitor the blood glucose hourly and give a rapid analog according to the child's home glucose correction scale. If glargine is used as the basal insulin, a full dose is given the evening before planned surgery. If NPH, lente, or ultralente are used, one half of the morning dose is given before surgery. The child should not be discharged until blood glucose levels are stable and oral intake is tolerated.

Long-Term Complications: Relation to Glycemic Control. The increasingly prolonged survival of the diabetic child is associated with an increasing prevalence of complications. Complications of DM can be divided into three major categories—(1) microvascular complications, specifically retinopathy and nephropathy; (2) macrovascular complications, particularly accelerated coronary artery disease, cerebrovascular disease, and peripheral vascular disease; and (3) neuropathies, both peripheral and autonomic, affecting a variety of organs and systems. Cataracts affect the lens.

Diabetic retinopathy is the leading cause of blindness in the United States in adults aged 20–65 yr. The risk of diabetic retinopathy after 15 yr duration of diabetes is 98% for individuals with type 1 DM and 78% for those with type 2 DM. Lens opacities (due to glycation of tissue proteins and activation of polyol pathway) are present in at least 5% of those younger

TABLE 583–11. Guidelines for Intravenous Insulin Coverage During Surgery

Blood Glucose Level (mg/dL)	Insulin Infusion (units/kg/hr)	Blood Glucose Monitoring
<120	0.00	1 hr
121–200	0.03	2 hr
200–300	0.06	2 hr
300–400	0.08	1 hr*
400	0.10	1 hr*

An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times maintenance rate.

*Check urine ketones.

than 19 yr of age. Although the metabolic control has an impact on the development of this complication, genetic factors also have a role, because only 50% of patients develop proliferative retinopathy. The earliest clinically apparent manifestations of diabetic retinopathy are classified as nonproliferative or background diabetic retinopathy—microaneurysms, dot and blot hemorrhages, hard and soft exudates, venous dilation and beading, and intraretinal microvascular abnormalities. These changes do not impair vision. The more severe form is proliferative diabetic retinopathy—manifested by neovascularization, fibrous proliferation, and preretinal and vitreous hemorrhages. Proliferative retinopathy, if not treated, is relentlessly progressive and impairs vision, leading to blindness. The mainstay of treatment is panretinal laser photocoagulation. In advanced diabetic eye disease—manifested by severe vitreous hemorrhage or fibrosis, often with retinal detachment—vitrectomy is an important therapeutic modality. Eventually, the eye disease becomes quiescent, a stage termed *involutional retinopathy*. A separate subtype of retinopathy is diabetic maculopathy, which is manifested by severe macular edema impairing central vision, for which focal laser photocoagulation may be effective.

Guidelines suggest that diabetic patients have an initial dilated and comprehensive examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with type 2 DM, and within 3–5 yr after the onset of type 1 DM (but not before age 10 yr). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both type 1 and type 2 DM patients should be repeated annually by an ophthalmologist who is experienced in diagnosing the presence of diabetic retinopathy and is knowledgeable about its management.

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States. Most ESRD from diabetic nephropathy is preventable. Diabetic nephropathy affects 20–30% of patients with type 1 DM and 15–20% of type 2 DM patients 20 yr after onset. The mean 5-yr life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term type 1 DM may be due to nephropathy, which may account for about 50% of deaths. The risk of nephropathy increases with duration of diabetes, up until 25–30 yr duration (after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Only 30–40% of patients affected by type 1 DM eventually experience ESRD. The glycation of tissue proteins results in glomerular basement membrane thickening. The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate (AER) of 30–300 mg/24 hr (20–200 µg/min)—so-called microalbuminuria—can be detected and constitutes an early stage of nephropathy from intermittent to persistent (incipient), which is commonly associated with glomerular hyperfiltration and blood pressure elevation. As nephropathy evolves to early overt stage with proteinuria (AER > 300 mg/24 hr or > 200 µg/min), it is

accompanied by hypertension. Advanced stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and hypertension. Progression to ESRD is recognized by the appearance of uremia, the nephritic syndrome, and the need for renal replacement (transplantation or dialysis).

Screening for diabetic nephropathy is a routine aspect of diabetes care. The American Diabetes Association (ADA) recommends yearly screening for individuals with type 2 DM and yearly screening for those with type 1 DM after 5 yr duration of disease (but not before puberty). Twenty-four hour AER (urinary albumin and creatinine) or timed (overnight) urinary AER are acceptable techniques. Positive results should be confirmed by a second measurement of AER because of the high variability of albumin excretion in patients with diabetes. Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevation urinary albumin excretion. There is marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3–6 mo period should show elevated levels before a patient is diagnosed with microalbuminuria and treatment is started. Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys: (1) meticulous control of hyperglycemia, (2) aggressive control of systemic blood pressure, (3) selective control of arteriolar dilation by use of angiotensin-converting enzyme (ACE) inhibitors (thus decreasing transglomerular capillary pressure), and (4) dietary protein restriction (because high protein intake increases renal perfusion rate).

Diabetic Neuropathy. Both the peripheral and autonomic nervous systems can be involved, and adolescents with diabetes can show early evidence of neuropathy. This complication can be traced to the metabolic effects of hyperglycemia and/or other effects of insulin deficiency on the various constituents of the peripheral nerve. The polyol pathway, nonenzymatic glycation, and/or disturbances of myoinositol metabolism affecting one or more cell types in the multicellular constituents of the peripheral nerve appear likely to have an inciting role. The role of other factors, such as possible direct neurotrophic effects of insulin, insulin-related growth factors, nitric oxide, and stress proteins, seems to be relevant. Peripheral neuropathy may first present in some adolescents with long-standing history of diabetes. Using quantitative sensory testing (QST), abnormal cutaneous thermal perception is a common finding in both upper and lower limbs in neurologically asymptomatic young diabetic patients. Heat-induced pain threshold in the hand is correlated with the duration of the diabetes. There is no correlation between QST scores and metabolic control. Subclinical motor nerve impairment as manifested by reduced sensory nerve conduction velocity and sensory nerve action potential amplitude can be detected during late puberty and after puberty in about 10% of adolescents. Poor metabolic control during puberty appears to induce deteriorating peripheral neural function in young patients. An early sign of autonomic neuropathy such as decreased heart rate variability may present in adolescents with a history of long-standing disease and poor metabolic control. A number of therapeutic strategies have been attempted with variable results. These treatment modalities include (1) improvement in metabolic control, (2) use of aldose reductase inhibitors to reduce by-products of polyol pathway, (3) use of α -lipoic acid (an antioxidant) that enhances tissue nitric oxide and its metabolites, and use of anticonvulsants (e.g., lorazepam, valproate, carbamazepine, tiagabine, and topiramate) for treatment of neuropathic pain.

Other complications in diabetic children include dwarfism associated with a glycogen-laden enlarged liver (Mauriac syndrome), osteopenia, and a *syndrome of limited joint mobility* associated with tight, waxy skin, growth impairment, and maturational

delay. The Mauriac syndrome is related to under-insulinization; it is rare because of the availability of the longer-acting insulins. Clinical features of Mauriac syndrome include moon face, protuberant abdomen, proximal muscle wasting, and enlarged liver due to fat and glycogen infiltration. The syndrome of limited joint mobility is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and nephropathy, which may appear before 18 yr of age.

Prognosis. Type 1 DM is not a benign disease. It has been estimated that average life span of individuals with diabetes is about 10 yr shorter than nondiabetic population. Visual, renal, neuropathic, and other complications were relatively frequent. Furthermore, although diabetic children eventually attain a height within the normal adult range, puberty may be delayed, and the final height may be less than the genetic potential. From studies in identical twins, it is apparent that despite seemingly satisfactory control, the diabetic twin manifests delayed puberty and a substantial reduction in height when onset of disease occurs before puberty. These observations indicate that, in the past, conventional criteria for judging control were inadequate and that adequate control of type 1 DM was almost never achieved by routine means.

The introduction of portable devices (insulin pumps) that can be programmed to provide CSII with meal-related pulses is one approach to the resolution of these long-term problems. In selected individuals, nearly normal patterns of blood glucose and other indices of metabolic control, including HbA_{1c}, have been maintained for several years. This approach, however, should be reserved for highly motivated persons committed to rigorous self-monitoring of blood glucose, who are alert to the potential complications such as mechanical failure of the infusion device causing hyperglycemia or hypoglycemia and to infections at the site of catheter insertion.

The changing pattern of metabolic control is having a profound influence on reducing the incidence and the severity of certain complications. For example, after 20 yr of diabetes, there is a decline in the incidence of nephropathy in type 1 DM in Sweden among children diagnosed in 1971–1975 compared with those diagnosed in the preceding decade. Also, in most patients with microalbuminuria in whom it was possible to obtain good glycemic control, microalbuminuria disappeared. Thus, prognosis is related to metabolic control.

Pancreas and Islet Transplantation and Regeneration. In an attempt to cure type 1 DM, transplantation of a segment of the pancreas or of isolated islets has been performed. These procedures are both technically demanding and associated with the risks of disease recurrence and complications of rejection and its treatment by immunosuppression. Hence, segmental pancreas transplantation is generally performed in association with transplantation of a kidney for a patient with ESRD due to diabetic nephropathy in which the immunosuppressive regimen is indicated for the renal transplantation. Several thousand such transplants have been performed in adults. With experience and newer immunosuppressive agents, functional survival of the pancreatic graft may be achieved for up to several years, during which time patients may be in metabolic control with no or minimal exogenous insulin and reversal of some of the microvascular complications. However, because children and adolescents with DM are not likely to have ESRD from their diabetes, pancreas transplantation as a primary treatment in children cannot be recommended or its risk justified. Complications of immunosuppression include the development of malignancy. Some antirejection drugs, notably cyclosporine and tacrolimus, are themselves toxic to the islets of Langerhans, impairing insulin secretion and even causing diabetes. Attempts to transplant isolated islets have been equally challenging because of rejection. Research continues to improve techniques for the yield, viability, and reduction of immunogenicity of the islets of Langerhans for transplantation.

An islet transplantation strategy (Edmonton-protocol) infuses isolated pancreatic islets into the portal vein of a group of adults with type 1 DM. This therapeutic strategy also involved the use of a new generation of immunosuppressive medications that apparently have lower side-effect profiles than other drugs. Out of 15 consecutive patients with at least 1 yr of follow-up after the initial transplant, 12 (80%) were insulin independent at 1 yr. Although patients experienced minimal side effects from immunosuppressive medications, some complications associated with islet transplantation procedures were observed that included portal vein thrombosis, bleeding related to the percutaneous portal vein access, an expanding intrahepatic and subscapular hemorrhage on anticoagulation (requiring transfusion and surgery). Elevated liver function test results were found in 46% of subjects but resolved in all.

Regeneration of islets is an approach that could potentially cure type 1 DM. It is classified into three categories:

1. In vitro therapy using transplanted cultured cells, including embryonic stem cells, pancreatic stem cells, and β cell lines, in conjunction with immunosuppressive therapy or immunoisolation.
2. Ex vivo regeneration therapy, patients' own cells, such as bone marrow stem cells, which are transiently removed and induced to differentiate into β cells in vitro. At present, however, insulin-producing cells cannot be generated from bone marrow stem cells.
3. In vivo regeneration therapy, in which impaired tissues regenerate from patients' own cells in vivo. β -cell neogenesis from non- β cells and β -cell proliferation in vivo has been considered, particularly as regeneration therapies for type 2 DM.

Regeneration therapy of pancreatic β cells can be combined with various other therapeutic strategies, including islet transplantation, cell-based therapy, gene therapy, and drug therapy to promote β -cell proliferation and neogenesis, and it is hoped that these strategies will, in the future, provide a cure for diabetes.

583.3 Type 2 Diabetes Mellitus

Type 2 DM is considered a polygenic disease aggravated by environmental factors, such as low physical activity or hypercaloric lipid-rich diet. Obese type 2 diabetic patients show insulin resistance of skeletal muscle, enhanced hepatic glucose production, and decreased glucose-induced insulin secretion. Over time, hyperglycemia worsens, a phenomenon that has been attributed to deleterious effect of chronic hyperglycemia (glucotoxicity) or chronic hyperlipidemia (lipotoxicity) on β -cell function and is often accompanied by increased triglyceride content and decreased insulin gene expression. This category of diabetes has been considered a disease of obese and sedentary adults after age 40 yr. Numerous studies describe type 2 DM in Native American youth, as well as their African American, Hispanic, and white peers. Pediatric type 2 DM in adolescents represents one of the most rapidly growing forms of diabetes. The incidence of type 2 DM among children diagnosed with diabetes at one medical center increased from 4% before 1992 to 16% in 1994. In that report, among those aged 10–19 yr, type 2 DM accounted for one third of all newly diagnosed children with diabetes in 1994. Overall, the incidence of adolescent type 2 DM increased 10-fold from 0.7 to 7.2/100,000 per year in the reported Midwest metropolitan area. The mean age of presentation was 13.8 yr; most children were markedly obese. We have observed a more than 10-fold increase in incidence of type 2 DM (from less than 2% to about 22% of new cases of DM) in children aged 10–18 yr in the past decade. African American, Hispanic, and white adolescents are usually affected. African Americans constitute almost 70% of the type 2 DM cases.

The epidemic of type 2 DM in children and adolescents parallels the emergence of the obesity epidemic. Although obesity itself is associated with insulin resistance, diabetes does not develop until there is some degree of failure of insulin secretion. Thus, when measured, insulin secretion in response to glucose or other stimuli is always lower in persons with type 2 DM than in control subjects matched for age, sex, weight, and equivalent glucose concentration. Although it is generally believed that autoimmune destruction of pancreatic β cells does not occur in type 2 DM diabetes, autoimmune markers of type 1 DM, namely GAD65, ICA512, and IAA may be positive in up to one third of the cases of adolescent type 2 DM. These findings reflect a broad spectrum of pancreatic and peripheral abnormalities that could lead to type 2 DM and the presence of these autoimmune markers does not rule out type 2 DM in children and adolescents.

In type 2 DM, insulin deficiency is rarely absolute, so patients usually do not need insulin to survive, although glycemic control may be improved by exogenous insulin. DKA, when it occurs, is associated with the stress of another illness such as severe infection and may resolve when the stressful illness resolves. DKA tends to be more common in African American patients than in other ethnic groups. Most patients with type 2 DM remain asymptomatic for months to years because hyperglycemia is so moderate that symptoms are not as dramatic as the polyuria and weight loss accompanying type 1 DM; weight gain may continue. The prolonged hyperglycemia may be accompanied, in time, by the development of microvascular and macrovascular complications. Type 2 DM occurs more frequently in certain ethnic or racial groups, such as Pacific Islanders, Pima Indians, and African Americans. It also occurs in individuals with hypertension and dyslipidemia. Type 2 DM has a stronger genetic component than in type 1 DM. Concordance rates among identical twins are virtually 100% for type 2 and only 30–50% for type 1 DM. The genetic basis for type 2 DM is complex and incompletely defined; no single identified defect predominates as does the HLA association with type 1 DM. *Acanthosis nigricans* may be a marker for insulin resistance, hyperinsulinemia, and eventually type 2 DM. Hirsutism, associated with the *polycystic ovary syndrome*, premature adrenarche, or mild mutations in steroidogenic enzymes, is frequently associated with insulin resistance in children and adolescents and may be a forerunner of the future development of type 2 DM (see Chapter 580).

Type A insulin resistance with acanthosis nigricans is characterized by severe insulin resistance and acanthosis nigricans in the absence of obesity or lipoatrophy; affected females also have hyperandrogenism, possibly as a secondary manifestation of the hyperinsulinemia with stimulation of androgen synthesis by ovarian theca cells (see Chapter 580). Glucose intolerance is variable and includes symptomatic diabetes. The hyperandrogenism presents with clinical and biochemical findings suggestive of polycystic ovary syndrome. Some patients, predominantly African American females with obesity, acanthosis nigricans, and accelerated growth suggestive of gigantism, may represent insulin resistance due to obesity with downregulation of the insulin receptor. The gigantism may represent a “spillover” effect of insulin acting via the insulin growth factor 1 receptor rather than as the insulin receptor.

Treatment. Nutritional education is a cornerstone of therapy for children and adolescents with type 2 DM. These children often come from a household environment with a poor understanding of healthy eating habits. Commonly observed behaviors include skipping meals, heavy snacking, and excessive daily television viewing, video game playing, and computer use. Adolescents engage in non-appetite-based eating (i.e., emotional eating, television-cued eating, boredom) and cyclic dieting (“yo-yo”). Treatment for type 2 DM should target weight

loss and increasing physical activity as an initial approach. These approaches, however, are frequently unsuccessful.

The only universally accepted pharmacologic agent available for type 2 DM in children is insulin. Although optimal glycemic control can be obtained with insulin therapy, it often results in significant weight gain. At the time of diagnosis and depending on presentation, insulin therapy may be necessary, but with close medical follow-up, it can often be reduced, substituted, or even discontinued within a few weeks after glucose control is achieved. Once a patient is nonacidotic and well hydrated, an effective therapy is to initiate insulin management in combination with metformin (a biguanide), which decreases hepatic glucose production. The starting dose of metformin is usually 500 mg, twice daily with meals. Metformin is contraindicated if there is significant renal or liver impairment. Therefore, proper assessment of liver and renal function is essential before initiating therapy. A class of pharmaceutical agents, the thiazolidinediones, enhances insulin action by decreasing hepatic glucose production and facilitating glucose disposal in muscle and fat. Because they act as insulin enhancers, they are used in conjunction with exogenous insulin and metformin. These agents, the "glitazones," are not approved for use in children in the United States; undue liver toxicity has been reported.

Prevention. The difficulties in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for type 2 DM, which is clearly linked to modifiable risk factors, i.e., obesity, and a sedentary lifestyle. The Diabetes Prevention Program (DPP) was designed to prevent or delay the development of type 2 DM in adult individuals at high risk for its development by virtue of their having impaired glucose tolerance (IGT). The DPP results demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of type 2 DM. The results were striking. Lifestyle intervention reduced diabetes incidence by 58%; metformin reduced the incidence by 31% compared with placebo. The effects were similar for men and women and for all racial and ethnic groups. Lifestyle interventions are believed to have similar beneficial effects in obese adolescents with IGT.

Impaired Glucose Tolerance. The term *impaired glucose tolerance* (IGT) is suggested as a replacement for terms such as asymptomatic diabetes, chemical diabetes, subclinical diabetes, borderline diabetes, or latent diabetes in order to avoid the stigma associated with the term *diabetes mellitus*, which may influence the choice of vocation, eligibility for health or life insurance, and self-image. Although IGT represents a biochemical intermediate between normal glucose metabolism and that of diabetes, experience has shown that few children with IGT go on to acquire diabetes; estimates range from 0–10%. There is disagreement about whether the degree of glucose intolerance is useful as a prognostic index of the likelihood of progression, but there is evidence that among the few instances of progression, the insulin response during glucose tolerance testing is severely impaired. Islet cell or insulin autoantibodies as well as the HLA-DR3 or -DR4 haplotype are commonly found in those who go on to develop clinical diabetes. In most obese children with IGT, insulin responses during oral glucose tolerance tests are higher than the mean for age-adjusted but not weight-adjusted control subjects; these individuals have some resistance to the effects of insulin rather than a total inability to secrete it.

In healthy nondiabetic children, the glucose response during an oral glucose tolerance test is similar at all ages. In contrast, plasma insulin responses during the test increase progressively within the age span of about 3–15 yr and are significantly higher during puberty so that interpretation of these responses requires comparison with age- and puberty-adjusted responses.

The performance of the glucose tolerance test should be standardized according to currently accepted criteria. These include

at least 3 days of a well-balanced diet containing approximately 50% of calories from carbohydrates, fasting from midnight until the time of the test in the morning, and a dose of glucose for the test of 1.75 g/kg but not more than 75 g. Plasma samples are obtained before ingestion of the glucose and at 1, 2, and 3 hr thereafter. The arbitrarily designated response to the test that identifies IGT is a fasting plasma glucose value of less than 126 mg/dL and a value at 2 hr of more than 140 mg/dL but less than 200 mg/dL (see Table 583–2). Determination of serum insulin responses during the glucose tolerance test is not a prerequisite for reaching a diagnosis; the magnitude of the response, however, may have prognostic value.

In children with IGT but without fasting hyperglycemia, repeated oral glucose tolerance tests are not recommended. Investigations in such children indicate that the degree of impaired glucose tolerance tends to remain stable or may actually improve over a period of years, except in patients with markedly subnormal insulin responses. Consequently, apart from reduction in weight for the obese child, no therapy is indicated. In particular, the use of oral hypoglycemic agents should be restricted to investigational studies. If fasting hyperglycemia or characteristic symptoms of diabetes develop, the affected children have the characteristics of type 2 DM, previously known as NIDDM (see Table 583–1).

583.4 Other Specific Types of Diabetes

Genetic Defects of β -Cell Function

MATURITY-ONSET DIABETES OF YOUTH. This subtype of DM contains a group of heterogeneous genetic and clinical entities, which are characterized by early onset between the ages of 9 and 25 yr of age, autosomal dominant inheritance (AD), and a primary defect in insulin secretion. Three types of maturity-onset diabetes of youth (MODY) genes have been identified. MODY 1 results from a mutation in the hepatocyte nuclear factor (HNF)-4 α gene located on the long arm of chromosome 20. MODY 2 is caused by a mutation in the gene for glucokinase located on the short arm of chromosome 7. MODY 3 is due to a gene mutation for HNF-1 α located on the long arm of chromosome 12. Strict criteria for the diagnosis of MODY include diabetes in at least three generations with AD transmission and diagnosis before age 25 yr in at least one affected subject.

Mutations in the glucokinase gene responsible for MODY 2 result in mild, chronic hyperglycemia due to mild reductions in pancreatic β -cell response to glucose. As a result, this is usually a relatively mild form of diabetes with mild fasting hyperglycemia and IGT in the majority of patients, which can be treated with small doses of exogenously administered insulin. Patients affected with mutations in HNF-4 α or -1 α show more severe abnormalities of carbohydrate metabolism, varying from impaired glucose tolerance to severe diabetes and often progressing from a mild to a severe form over time. About one third of these patients will require insulin and are prone to the development of vascular complications. Patients with MODY 2 and defects in the glucokinase gene may demonstrate normal insulin responses to intravenous glucose when blood glucose concentrations are maintained at greater than 7 mM. Defective glucokinase activity has been likened to a defective glucose sensor in the pancreatic β cell. By contrast, patients with MODY 1 and MODY 3 have more severe impairment of insulin secretion, and this defect cannot be overcome by priming with glucose infusion.

By definition, the absence of a family history suggestive of AD inheritance makes a diagnosis of MODY virtually untenable. In such circumstances, the appearance of diabetes in a relatively young person would most likely represent evolving type 1 DM,

and therefore evaluation for markers of autoimmunity are warranted. Milder, slowly evolving type 1 DM could be confused with type 2 DM.

Distinction among the present forms of MODY has clinical relevance in counseling because of the lesser likelihood of vascular complications in MODY 2 and, therefore, the need to treat appropriately with insulin, if necessary, in patients with MODY 1 and MODY 3. Molecular analysis for the currently known gene mutations on chromosomes 20, 7, and 12 are likely to become available for routine clinical use in the future to facilitate diagnosis and management. An additional form of MODY due to heterozygous mutation in a homeodomain transcription factor called insulin promoter factor-1 has also been described.

Primary or secondary defects in *GLUT-2 type of glucose transporter*, an insulin-independent form, may also be associated with diabetes. GLUT-2 rapidly transports glucose into β cells for subsequent phosphorylation by glucokinase, which eventually leads to insulin secretion. The phenomenon of glucose toxicity, in which there is a loss or reduction in the first-phase insulin response to a pulse of glucose, may be the result of secondary downregulation of GLUT-2 transporters.

MODY also may be a manifestation of a *polymorphism in the glycogen synthase gene*. This enzyme is crucially important for storage of glucose as glycogen in muscle. Patients with this defect are notable for marked resistance to insulin and hypertension as well as a strong family history of diabetes.

MITOCHONDRIAL GENE DEFECTS. Point mutations in mitochondrial DNA are sometimes associated with DM and deafness. One mutation is identical to the mutation in MELAS (myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome), but this syndrome is not associated with diabetes so that the phenotypic expression of the same defect varies. Another form of IDDM, sometimes associated with mitochondrial mutations, is the Wolfram syndrome.

Wolfram syndrome is characterized by diabetes insipidus, DM, optic atrophy, and deafness—thus the acronym DIDMOAD. Wolfram syndrome is caused by mitochondrial dysfunction, possibly by a nuclear gene mapped to the short arm of chromosome 4. Some patients with diabetes appear to have severe insulinopenia, whereas others have significant insulin secretion as judged by C-peptide. In two patients who were tested, islet cell antibodies were not detected, whereas HLA typing revealed DR2, which is generally considered “protective” for diabetes. In some patients with diabetes and deafness, a mutation in mitochondrial tRNA has been detected; in others, this mutation is absent. The overall prevalence is 1/770,000. The sequence of appearance of the stigmata was as follows: nonautoimmune IDDM in the 1st decade; central diabetes insipidus and sensorineural deafness in two thirds to three fourths of the patients in the 2nd decade; renal tract anomalies in about one half of the patients in the 3rd decade; and neurologic complications such as cerebellar ataxia and myoclonus in one half to two thirds of the patients in the 4th decade. Other features included primary gonadal atrophy in the majority of males and a progressive neurodegenerative course with neurorespiratory death at a median age of 30 yr. Absence of maternal diabetes or deafness and absence of the previously reported mitochondrial gene defect suggests autosomal recessive inheritance.

DIABETES MELLITUS OF THE NEWBORN

Transient. Onset of persistent type 1 DM before the age of 6 mo is most unusual. The syndrome of transient DM in the newborn infant has its onset in the 1st wk of life and persists only several weeks to months before spontaneous resolution. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and, at times, metabolic acidosis but with only minimal or no ketonemia or ketonuria. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations are normal. After sponta-

neous recovery, the insulin responses to these same stimuli are brisk and normal, implying a functional delay in β -cell maturation with spontaneous resolution. Occurrence of the syndrome in consecutive siblings has been reported. Abnormalities of chromosome 6 are common in transient neonatal DM. There are also reports of patients with classic type 1 DM who formerly had transient diabetes of the newborn. It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classic type 1 DM is a chance occurrence or causally related. This syndrome should be distinguished from severe hyperglycemia that may occur in hypertonic dehydration; this condition usually occurs in infants beyond the newborn period who respond promptly to rehydration with a minimal requirement for insulin.

Administration of insulin is mandatory during the active phase of DM in the newborn. One to 2 U/kg/24 hr of an intermediate-acting insulin in two divided doses usually results in dramatic improvement and accelerated growth and gain in weight. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifested or after 2 mo of age.

Permanent. DM in the newborn period may be permanent if associated with the rare syndrome of pancreatic agenesis. Long-term follow-up of a cohort of patients with neonatal diabetes revealed that almost one half had permanent diabetes, one third had transient diabetes, and about one fourth had transient diabetes that recurred when they were 7–20 yr old. The majority of all these infants were small at birth. Instances of affected twins and families with more than one affected infant have been reported. Some cases of permanent neonatal DM are initially euglycemic and present within the first month of life.

ABNORMALITIES OF THE INSULIN GENE. Diabetes of variable degrees may also result from *defects in the insulin gene* from faulty processing of proinsulin to insulin, an autosomal dominant defect, to various amino acid substitutions that impair the effectiveness of insulin at the receptor level. However, these defects are notable for the high concentration of insulin as measured by radioimmunoassay, whereas defects in glucokinase, MODY-1, MODY-3, and GLUT-2 are characterized by relative or absolute deficiency of insulin secretion for the prevailing glucose concentrations.

Genetic Defects of Insulin Action. Two mutations in the insulin receptor gene with relevance for children are leprechaunism and Rabson-Mendenhall syndrome.

LEPRECHAUNISM. This is a syndrome characterized by intrauterine growth retardation, fasting hypoglycemia, and postprandial hyperglycemia in association with profound resistance to insulin, whose serum concentrations may be 100-fold that of comparable age-matched infants during an oral glucose tolerance test. Various defects of the insulin receptor have been described, thereby attesting to the important role of insulin and its receptor in fetal growth and possibly in morphogenesis. However, even probable complete absence of functional insulin receptors due to homozygous inheritance of a missense mutation in the insulin-receptor gene resulted in normal organogenesis and a liveborn infant who had a severe form of leprechaunism. Most of these patients die in the 1st yr of life.

RABSON-MENDENHALL SYNDROME. This entity is defined by clinical manifestations that appear to be intermediate between those of acanthosis nigricans with insulin resistance type A and leprechaunism. The features include extreme insulin resistance, acanthosis nigricans, abnormalities of the teeth and nails, and pineal hyperplasia. It is not clear whether this syndrome is entirely distinct from leprechaunism; however, patients with Rabson-Mendenhall tend to live beyond the 1st yr of life. Defects in the insulin-receptor gene have been described in this syndrome.

Cystic Fibrosis-Related Diabetes. Because of improvements in the medical care of children with cystic fibrosis (CF), many survive

to the late teenage and early adult years. On the other hand, as the annual screening of patients for diabetes among CF centers has become routine, the number of CF-related diabetes (CFRD) cases has almost more than doubled. It is estimated that up to 25% of adolescents with CF have diabetes. The care of these patients is very different from that of patients with type 1 or type 2 DM, because CFRD patients have distinct pathophysiology and complicated nutritional and medical problems.

Patients with CFRD are slender and have insulin deficiency. The clinical presentation is similar to that of type 2 DM in that the onset of the disease is insidious and the occurrence of ketoacidosis is rare. Islet antibody titers are negative. The prevalence of microvascular complications in CFRD in relationship to duration of diabetes, glycemic control, and pulmonary diseases are not well characterized. Macrovascular complications do not appear to be of concern in CFRD. Several factors unique to CF influence both the onset and the course of diabetes: (1) frequent acute or chronic infections are associated with waxing and waning of insulin resistance; (2) energy needs are increased because of infection and pulmonary disease; (3) malnutrition is associated with poor survival; (4) malabsorption is caused by pancreatic exocrine insufficiency, despite enzyme supplementation; (5) altered nutrient absorption is caused by abnormal intestinal transit time; (6) liver disease is present; (7) anorexia and nausea are common as a result of illness, gastroesophageal reflux, delayed gastric emptying, intestinal obstruction, increased work of breathing, and psychosocial factors; (8) there is a wide variation in daily food intake based on the patient's acute health status; and (9) insulin and glucagon secretion are impaired.

In the pancreas, exocrine tissue is replaced by fibrosis and fat; many of the pancreatic islets are destroyed. The remaining islets demonstrate diminished numbers of β -, α -, and pancreatic polypeptide-secreting cells. Secretion of the islet hormones insulin, glucagon, and pancreatic polypeptide is impaired in patients with CF in response to a variety of secretagogues. It has been suggested that insulin resistance may also play a role in the development of CFRD, especially in the setting of acute infection.

In Denmark, oral glucose tolerance screening of the entire CF population demonstrated no diabetes in patients younger than 10 yr, 12% diabetes in patients aged 10–19 yr, and 48% diabetes in adults aged 20 yr and older. At a Midwestern center where routine annual oral glucose tolerance screening is performed, only about one half of children and one fourth of adults have normal glucose tolerance. Diabetes is seen in 9% of CF children, 26% of adolescents, and 35% of adults aged 20–29 yr. About one third of patients with CFRD have fasting hyperglycemia and two thirds have CFRD without fasting hyperglycemia. The fasting hyperglycemia is exacerbated chronically, or intermittently with infection or glucocorticoid therapy in 3% of children, 11% of adolescents, and 15% of adults.

When hyperglycemia develops, the accompanying metabolic derangements are usually mild and, if insulin therapy becomes necessary, relatively low doses usually suffice for adequate management. Ketoacidosis is uncommon but may occur with progressive deterioration of islet cell function. Treatment with insulin is as outlined for type 1 DM, but dietary management may be limited by the constraints of the primary disturbance.

Autoimmune Diseases. *Chronic lymphocytic thyroiditis* (*Hashimoto thyroiditis*) is frequently associated with type 1 DM in children (Chapter 559). As many as one in five insulin-dependent diabetic patients may have thyroid antibodies in their serum; the prevalence is 2–20 times greater than that observed in control populations. Only a small proportion of these patients, however, acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 yr. Periodic palpation of the thyroid gland is indicated in all diabetic children; if the gland feels firm or enlarged, or both, serum measurements of thy-

roid antibodies and thyroid-stimulating hormone (TSH) should be obtained. A TSH level of greater than 10 μ U/mL indicates existing or incipient thyroid dysfunction that warrants replacement with thyroid hormone. Deceleration in the rate of growth may also be due to thyroid failure and is, in itself, a reason for securing serum measurements of thyroxine and TSH concentrations.

When diabetes and thyroid disease coexist, the possibility of *adrenal insufficiency* should also be considered. It may be heralded by decreasing insulin requirements, increasing pigmentation of the skin and buccal mucosa, salt craving, weakness, asthenia and postural hypotension, or even frank Addisonian crisis as evidence of primary adrenal failure. This syndrome is most unusual in the 1st decade of life, but it may become apparent in the 2nd decade or later.

Celiac disease, formerly known as nontropical sprue, another autoimmune disorder, is due to hypersensitivity to dietary gluten that occurs with significant frequency in children with type 1 DM (Chapter 320.8). It is estimated that about 7.0% of children with type 1 DM develop celiac disease within the first 6 yr from the diagnosis. Young children with type 1 DM and celiac disease usually present with gastrointestinal symptoms (abdominal cramping, diarrhea, and gastroesophageal reflux), growth failure due to suboptimal weight gain, and unexplained hypoglycemic reactions due to nutrient malabsorption, whereas adolescents may remain asymptomatic for the most part. The diagnosis of celiac disease is considered if serum antiendomysial and/or tissue transglutaminase antibody titers are positive in the presence of normal serum total IgA level. However, the diagnosis is confirmed on endoscopic evaluation and biopsy of small bowel revealing characteristic histopathologic (atrophic) changes of intestinal villi.

Circulating antibodies to gastric parietal cells and to intrinsic factor are two to three times more common in patients with type 1 DM than in control subjects. There are good correlations of antibodies to gastric parietal cells with atrophic gastritis and of antibodies to intrinsic factor with *malabsorption of vitamin B₁₂*. Although the possibility of megaloblastic anemia should be considered in children with type 1 diabetes, its occurrence is rare.

A *variant of the multiple endocrine deficiency syndrome* is characterized by type 1 diabetes-idiopathic intestinal mucosal atrophy with associated inflammation and severe malabsorption, IgA deficiency, and circulating antibodies to multiple endocrine organs including the thyroid, adrenal, pancreas, parathyroid, and gonads. In addition, nondiabetic family members have an increased frequency of vitiligo, Graves disease, and multiple sclerosis as well as low complement levels and antibodies to endocrine tissues.

Endocrinopathies. The endocrinopathies listed in Table 583–1 are only rarely encountered as a cause of diabetes in childhood. They may accelerate the manifestations of diabetes in those with inherited or acquired defects in insulin secretion or action.

Drugs. The immunosuppressive agents cyclosporin and tacrolimus are toxic to β cells, causing IDDM in a significant proportion of patients treated with these agents. Their toxicity to pancreatic β cells was a contributing factor in limiting their usefulness to arrest ongoing autoimmune destruction of β cells. Streptozotocin and the rodenticide Vacor also are toxic to β cells, causing diabetes.

Genetic Syndromes Associated with Diabetes Mellitus. A number of rare genetic syndromes associated with IDDM or carbohydrate intolerance have been described (see Table 583–1). These syndromes represent a broad spectrum of diseases ranging from premature cellular aging, as in the Werner and Cockayne syndromes (see Chapter 79), to excessive obesity associated with hyperinsulinism, resistance to insulin action, and carbohydrate intolerance as in the Prader-Willi syndrome (see Chapter 69). Some of these syndromes are characterized by primary distur-

bances in the insulin receptor or in antibodies to the insulin receptor without any impairment in insulin secretion. Although rare, these syndromes provide unique models to understand the multiple causes of disturbed carbohydrate metabolism from defective insulin secretion or from defective insulin action at the cell receptor or postreceptor level.

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