Type 1 Diabetes

Epidemiology and Pathology

The principal features of T1DM, contrasted with T2DM, are summarized in Table 66-4. The peak incidence occurs between the ages of 6 and 14 years, but onset in approximately half of patients with T1DM occurs after the age of 20. The role of genetic factors in T1DM risk is supported by an observed increased incidence of T1DM among family members of affected patients: approximately 5% in siblings, 6% in offspring of a diabetic father, and 2% in offspring of a diabetic mother. On a background of genetic risk factors, it is hypothesized that the immune destruction of beta cells is precipitated by environmental factors that still are not well understood but may include microbial, chemical, or dietary triggers (Fig. 66-1). The operation of a combination of genetic and environmental factors is thought to explain the high but not absolute concordance observed in monozygotic twins (30% to 50%).

The prevalence of T1DM varies substantially in different populations; for example, it is relatively high in northwestern Europe and much lower in parts of Asia. The overall prevalence in the United States is approximately 2.4 cases per 1000 population. The frequent onset before age 20 makes T1DM one of the most common chronic, serious childhood diseases. It is the most common subtype of diabetes in childhood, accounting for approximately 70% of all cases, with T2DM accounting for most of the remainder. LADA, a variant form of autoimmune T1DM, is characterized by onset in adulthood and a more prolonged waxing and waning course than is typical for T1DM.

The onset of overt T1DM follows a preclinical phase of variable duration (typically extending from months to years) during which there is specific destruction of beta cells resulting predominantly from cell-mediated immune mechanisms (mononuclear cells; mainly CD8+ T lymphocytes). It is believed that the autoantibodies (to islet cells, insulin, GAD, and tyrosine phosphatases) are generated for the most part in response to exposure of beta cells and islets and are not themselves mediators of the destructive process. Demonstration of one or more autoantibodies also represents the most sensitive and useful way to establish preclinical disease in patients at risk (e.g., first-degree relatives of patients with T1DM).

The complement of islets in a healthy individual normally provides enough excess beta cell secretory capacity to maintain blood glucose levels until 80% to 90% of beta cells have been lost. In some patients, the subclinical loss of beta cells may be unmasked, resulting in hyperglycemia during the course of an intercurrent illness such as an incidental upper respiratory tract infection. Hyperglycemia and even ketogenesis can result from a lack of adequate insulin, decreased glucose excretion due to hypovolemia, accelerated gluconeogenesis, increased insulin resistance, and hepatic ketogenesis. After diagnosis and institution of insulin and other therapy, stress-induced insulin resistance resolves, and there may be some degree of recovery of beta cell function. Some patients revert to a state in which no insulin is required. This phenomenon, designated the *honeymoon* period, lasts for several weeks to as long as 1 year. Patients generally should continue insulin administration at doses low enough to be tolerated during this interval, because progressive beta cell function can be expected eventually to result in recurrent hyperglycemia and, potentially, diabetic ketoacidosis (DKA).

Screening for T1DM is not a part of standard medical care. Screening for autoantibody determinations in individuals at risk is not clinically useful.

Clinical Presentation

T1DM most often manifests clinically with symptoms resulting from hyperglycemia and consequent osmotic diuresis. Patients typically have a history extending over days to weeks of worsening polyuria, plus polydipsia (as a compensatory response to

TABLE 66-4 GENERAL COMPARISON OF THE TWO MOST COMMON TYPES OF DIABETES MELLITUS

	TYPE 1	TYPE 2
Previous terminology	Insulin-dependent diabetes mellitus, type I; juvenile-onset diabetes	Non–insulin-dependent diabetes mellitus, type II; adult-onset diabetes
Age at onset	Usually <30 yr, particularly childhood and adolescence, but any age	Usually >40 yr, but increasingly at younger ages
Genetic predisposition	Moderate; environmental factors required for expression; 35-50% concordance in monozygotic twins; multiple candidate genes proposed	Strong; 60-90% concordance in monozygotic twins; many candidate genes proposed
Human leukocyte antigen associations	Linkage to DQA and DQB, influenced by DRB3 and DRB4 (DR2 protective)	None known
Other associations	Autoimmune; Graves' disease, Hashimoto's thyroiditis, vitiligo, Addison's disease, pernicious anemia	Heterogeneous group, ongoing subclassification based on identification of specific pathogenic processes and genetic defects
Precipitating and risk factors	Largely unknown; microbial, chemical, dietary, other	Age, obesity (central), sedentary lifestyle, previous gestational diabetes
Findings at diagnosis	85-90% of patients have one and usually more autoantibodies to ICA512, IA-2, IA-2β, GAD_{65}, IAA	Possibly complications (microvascular and macrovascular) caused by significant hyperglycemia in the preceding asymptomatic period
Endogenous insulin levels	Low or absent	Usually present (relative deficiency), early hyperinsulinemia
Insulin resistance	Only with hyperglycemia	Mostly present
Prolonged fast	Hyperglycemia, ketoacidosis	Euglycemia
Stress, withdrawal of insulin	Ketoacidosis	Nonketotic hyperglycemia, occasionally ketoacidosis

GAD, Glutamic acid decarboxylase; IA-2, IA-2β, insuloma-associated protein 2 and 2β (tyrosine phosphatases); IAA, insulin autoantibodies; ICA, islet cell antibody; ICA512, islet cell autoantigen 512 (fragment of IA-2).