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UPDATE

Update in Type 1 Diabetes

George S. Eisenbarth

Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Aurora, Colorado 80045

Context: Type 1 diabetes is a heterogeneous disorder characterized by severe β-cell loss. The great majority of patients have type 1A or immune-mediated diabetes.

Synthesis: There has been recent progress in defining the genetics, pathogenesis, and natural history of the disease. In addition, there is a major effort to develop immunotherapies to prevent the disorder and to cure the disease with islet transplantation, and there is potential for dramatic improvement in care with introduction of continuous glucose monitoring devices. The discovery of "metabolic memory" underscores the importance of excellent metabolic control. With comprehensive care, major microvascular complications (*e.g.* blindness and renal failure) are preventable for most patients.

Conclusion: The existence of multiple "competing" technologies to deal with this devastating disorder holds promise of improved outcomes. **(*J Clin Endocrinol Metab* 92: 2403–2407, 2007)**

AN AMERICAN DIABETES ASSOCIATION expert committee has proposed an etiologic classification of diabetes with type 1A diabetes representing immune-mediated diabetes and type 1B a non-autoimmune idiopathic form of type 1 diabetes (1). Additional diseases with severe β-cell deficiency with known genetic or environmental etiologies are categorized individually. The best current markers to distinguish type 1A diabetes from other forms of diabetes are the presence of anti-islet autoantibodies. Typically, autoantibodies reacting with glutamic acid decarboxylase (GAD65), insulin, and insulinoma antigen-2 are measured (2). Assays can be set such that each assay has a false-positive rate of approximately 1%, and together one or more of these autoantibodies are present in approximately 90% of new-onset patients (3) with type 1A diabetes. There are undoubtedly additional autoantigens to be defined, and a subset of patients lacking the above three islet autoantibodies express cytoplasmic islet cell autoantibodies measured with indirect immunofluorescent staining of human pancreas. This latter assay has however a long history of poor standardization, and, although it detects a subset of GAD65 and insulinoma antigen-2 autoantibodies, it does not detect anti-insulin autoantibodies.

It is now recognized that as many adults develop type 1 diabetes as children, and there is debate as to the classification of adults with clinical manifestations of type 2 diabetes who express anti-islet autoantibodies (most often GAD65 autoantibodies). Separate names have been given to this subgroup, such as LADA (latent autoimmune diabetes of the adult), but the group has human leukocyte antigen (HLA) alleles associated with typical type 1 diabetes (although decreased DR3/4-DQ8 heterozygosity that is associated with early onset of type 1A diabetes), and such patients as a group have accelerated loss of C-peptide secretion (4). There is evidence that some patients have insulin resistance as well as anti-islet autoimmunity, and there is no reason that type 2 and type 1A diabetes might not coexist. The genes controlling the development of type 1A diabetes do not increase risk of type 2 diabetes, and the major type 2 diabetes genetic polymorphism of TCF7L2 (transcription factor 7-like 2) is not associated with risk for type 1 diabetes (5).

Genetics

"Monogenic" inheritance

A mutation of the foxP3 (forkhead box P3) gene, a transcription factor that controls the development of regulatory T cells, is a cause of neonatal diabetes (6). The syndrome is termed IPEX syndrome (immune dysregulation, polyendocrinopthay, enteropathy, X-linked). As reflected in the name, children with the disorder suffer from overwhelming autoimmunity and usually die as infants. Of note, bone marrow transplantation can reverse disease. IPEX syndrome is rare, as is neonatal diabetes. In the differential diagnosis of neonatal diabetes, it must be recognized that half of children developing permanent neonatal diabetes have a mutation of the Kir6.2 molecule of the sulfonylurea receptor. These children with their non-autoimmune form of diabetes can be treated with oral sulfonylurea therapy.

Although more common than IPEX syndrome, the APS-1 syndrome (autoimmune polyendocrine syndrome type 1) is also rare. It results from a mutation of the AIRE (autoimmune regulator) gene, another transcription factor (7). Approximately 15% of patients with this syndrome develop autoimmune diabetes. The leading hypothesis as to etiology (*e.g.* Addison's disease, mucocutaneous candidiasis, and hypoparathyroidism) is that AIRE controls expression of autoantigens and negative selection of autoreactive T lymphocytes

Abbreviations: GAD, Glutamic acid decarboxylase; HLA, human leukocyte antigen.

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within the thymus. A very recent dramatic discovery is the demonstration that essentially 100% of patients with APS-1 have autoantibodies reacting with interferon α and other interferons. Such autoantibodies are extremely rare and essentially not found in patients with type 1 diabetes or Addison's disease outside of the syndrome.

Patients with type 1A diabetes and their relatives are at risk for development of thyroid autoimmunity, celiac disease, Addison's disease, pernicious anemia, and a series of other autoimmune disorders (8). Approximately 1 in 20 patients with type 1A diabetes have celiac disease by biopsy, although the majority have no symptoms (9). These asymptomatic individuals are usually detected with screening for transglutaminase autoantibodies. The level of transglutaminase autoantibodies relates to the probability of a positive biopsy, and it is important for clinicians to know the threshold for likely positive biopsy for the assay they use (10). There remains controversy as to whether asymptomatic celiac disease when detected should be treated with a gluten-free diet, and large clinical trials are needed to address this question.

Oligo/polygenic inheritance

Type 1A diabetes has become one of the most intensively studied polygenic disorders. The strongest associations with both susceptibility and protection from type 1A diabetes are HLA DR and DQ molecules. For instance, DQB1*0602 alleles are associated with dominant protection, and DR3-DQ2 molecules (DQB1*0201) and DR4-DQ8 (DQB1*0302) are associated with susceptibility (explanation of the nomenclature can be found in *Immunology of Type Diabetes*, available as an electronic book at www.barbaradaviscenter.org). Approximately 2% of newborns in Denver, Colorado are DR3/DR4 heterozygotes *vs.* 30% of children developing type 1A diabetes. The absolute risk of a child with this genotype developing type 1 diabetes from the general population is similar to a first-degree relative of a patient with type 1A diabetes (1 in 20). Within families, one can identify extreme risk of type 1 diabetes autoimmunity for children who both are DR3/DR4 heterozygotes and have inherited identical HLA haplotypes in common with their diabetic sibling (Fig. 1) (11).

Multiple additional genes are implicated as contributing to diabetes susceptibility, especially because whole-genome analysis is beginning to be applied to analysis of diabetes risk [CTLA4 (cytotoxic T-lymphocyte-associated protein 4), IFIH1 (interferon induced with helicase C domain 1), ITPR3 (inositol 1,4,5-triphosphate receptor 3), IL-2 receptor, PTPN22 (protein tyrosine phosphatase, nonreceptor type 22)].

Pathogenesis

Type 1A diabetes develops slowly, and progressive abnormalities in β-cell function herald what appears to be a sudden development of hyperglycemia. Rising HbA1c in the normal range (12), impaired fasting or glucose tolerance, as well as loss of first-phase insulin secretion usually precede overt diabetes. The exact β-cell mass remaining at diagnosis is poorly defined, and there are almost no studies of insulitis before diabetes onset (13). For patients with long-term type 1 diabetes, there is evidence of some β-cell function remaining (C-peptide secretion), although β-cell mass is usually

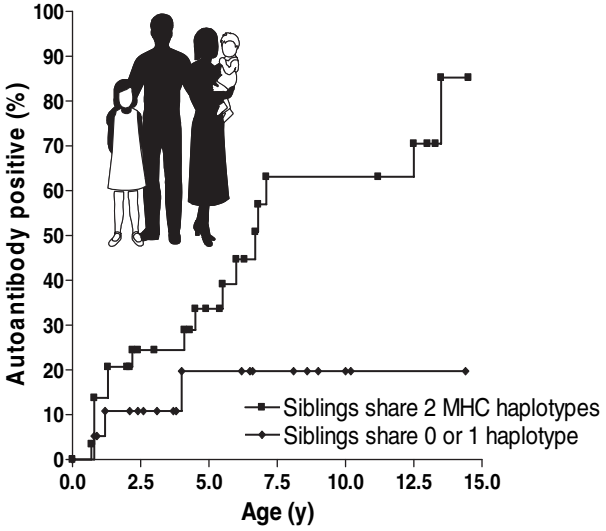

FIG. 1. Development of anti-islet autoantibodies among DR3/4-DQ8 siblings of patients with type 1 diabetes in the DAISY (Diabetes Autoimmunity Study in the Young) study with extreme risk for those sharing two HLA [major histocompatibility complex (MHC)] haplotypes with sibling proband (11). Figure was adapted from *Immunology of Type 1 Diabetes*, available as an electronic book at www.barbaradaviscenter.org.

decreased to less than 1% of normal (14). At present, methods to image/quantitate β-cell mass and insulitis are only beginning to be developed. In particular, positron emission tomography scanning using a labeled amine (dihydrotetrabenazine) may provide the first method to image islet mass (15), and this is now being evaluated in humans. A number of techniques are being evaluated to image insulitis (16).

A large body of evidence indicates that the development of type 1A diabetes is determined by a balance between pathogenic and regulatory T lymphocytes (17, 18). A fundamental question is whether there is a primary autoantigen for initial T cell autoreactivity with subsequent recognition of multiple islet antigens. A number of investigators have addressed in the NOD mouse (spontaneously develops type 1 diabetes) the importance of immune reactivity to insulin with the dramatic finding that eliminating immune responses to insulin blocks development of diabetes and insulitis and, importantly, immune responses to downstream autoantigens such as the islet-specific molecule IGRP (islet-specific glucose-6-phosphatase-related protein) (19). Knocking out both insulin genes (mice, in contrast to humans, have two insulin genes) with introduction of a mutated insulin with alanine rather than tyrosine at position 16 of the insulin B chain prevents development of diabetes (20). Recognition of this B-chain peptide of insulin by T lymphocytes depends on a "nonstringent" T cell receptor with conservation of only the α-chain sequence (Vα and Jα) and not the N-region of the α chain or the β chain (21).

A recent study of pancreatic lymph node from two patients with type 1 diabetes found a conserved T cell receptor, with T cells reacting with insulin A-chain peptide amino acids 1–15 (22).

Environmental Factors

The increasing incidence of type 1A diabetes strongly suggests that environmental factors are of importance. A leading hypothesis ("hygiene hypothesis") is that the increase may be attributable to lack of childhood infections (23). The major environmental factors being pursued include diet (*e.g.* bovine milk, cereals, insulin in milk, deficiency of vitamin D, or omega-3 fatty acids) and viruses (*e.g.* enteroviruses).

Prediction

It is now possible with a reasonable degree of accuracy to predict the development of type 1A diabetes. Although T lymphocytes are presumably causative, islet autoantibodies predict progression to disease. Assays for autoreactive T lymphocytes are improving, especially assays for CD8 T lymphocytes (24), but to date T cell assays have not been sufficiently validated for use in disease prediction.

A simple rule is that expression of at least two of the three islet autoantibodies (above) is highly predictive of progression to diabetes (25). This is true for both relatives of patients with type 1A diabetes and the general population. Identification of high risk of progression to diabetes in current research studies leads to early diagnosis and lack of hospitalization and usually lack of life-threatening ketoacidosis (26).

"Prevention" Trials

Multiple therapies that are being tested to prevent autoimmune β-cell destruction can be divided into primarily immunosuppressive or primarily immunoregulatory, with some therapies combining both features.

Immunosuppression

A TrialNet study of anti-IL-2 receptor antibody combined with 2 yr of therapy with mycophenolate mofetil has closed enrollment. Studies of anti-CD3 monoclonal antibodies at onset of type 1 diabetes found significant preservation of C-peptide secretion for at least 1 yr (27, 28). The anti-CD3 monoclonals were modified to reduce acute cytokine release, but there was evidence of transient activation of Epstein-Barr virus infection. There is considerable evidence that the anti-CD3 therapy is not simply immunosuppressive but induces longer-term changes in CD4/CD8 ratios and "regulatory" cells (29). Major questions remain as to the duration of therapeutic effect, whether a subset of individuals have long-term remission of β-cell destruction, and safety when larger numbers of individuals are treated. Rituximab, an anti-B-cell antibody that is effective in a number of autoimmune disorders, is being studied by TrialNet. Patients in North America can enquire concerning TrialNet prevention and new-onset studies by calling 1–800-HALT-DM1.

Immunoregulation

To date, large trials of nicotinamide, injections of insulin, and oral insulin have not demonstrated efficacy. A subset of individuals in the oral insulin prevention trial with high levels of insulin autoantibodies had an apparent several year delay in progression to diabetes, and a follow-up study is planned. A promising phase II trial of GAD65 injections for patients with new-onset diabetes has been reported on the Diamyd (Stockholm, Sweden) web site (www.diamyd.com). Most of the immunoregulatory therapies appear in animal models to act by inducing regulatory T lymphocytes (30), and direct cellular therapies can also prevent disease (31–34).

Therapy

Improved metabolic control

A series of modified human insulins that alter the dynamics of absorption after sc injection are now standards in clinical care, in particular regimens combining very-long-acting insulins with prandial rapidly absorbed insulins. Recently, inhaled insulin has become clinically available (rapid absorption) with recommendation that it be reserved for nonpregnant adults who are opposed to injections (35) pending longer-term safety data.

Islet/pancreatic transplantation

The publication by investigators at Edmonton of the dramatic efficacy of intensive immunosuppression combined with multiple infusions of islets from multiple donors stimulated the field of islet transplantation (36–39). Longer-term follow-up indicates that essentially all individuals lose graft function over time such that insulin therapy is again required within 5 yr (40). With introduction of continuous glucose monitors (see below), transplantation for hypoglycemia unawareness is likely to decrease. In contrast to islet transplantation, pancreatic transplantation often results in long-term reversal of diabetes but has associated surgical complications and complications related to immunosuppression.

The two major limitations for islet transplantation are the toxicity of immunosuppression and a lack of sufficient islet cells from cadaveric donors. Investigators are exploring xenogeneic transplantation with some success although using relatively toxic immunosuppressive regimens (41). There is a major world-wide effort to develop functional β cells and a tremendous increase in understanding of islet developmental biology with a long-term goal of stimulation of islet regeneration (42). There is important recent success with expansion of insulin-producing cells, but the expanded cells were unresponsive to glucose (43).

Continuous glucose monitors

A series of devices are now available (several are Food and Drug Administration approved) for the continuous measurement of sc glucose, including devices combining an insulin pump with a continuous glucose monitor (although not controlling the pump) (44–46). The current devices provide alarms (high or low), and continuous readings and studies are beginning to "close the loop," for instance, using such monitors to turn off insulin pumps at night if hypoglycemia is detected. A recent study indicates that improved target range glycemia can be achieved for patients with very elevated HbA1c as well as moderately elevated levels (with reduction in hypoglycemia) when patients receive real-time feedback of glucose levels (47).

Complications

The management of type 1A diabetes and modalities for prevention of complications has evolved, such that the majority of patients with excellent care and education should avoid major microvascular complications. The finding from the Diabetes Control and Complications Trial follow-up study of "metabolic memory," namely long-term benefit from early intensive glucose management, is very encouraging (48, 49). Intensive management and strict guidelines for lipid lowering and early introduction of renoprotective medications are the norm. Laser therapy for advanced retinal disease is also the norm, and "anti-vascular endothelial growth factor" ocular therapy for macular edema is being extensively studied. Effective prevention of microvascular complications requires detection of early lesions, including determination of lipids, blood pressure, microalbuminuria, and retinal exams. Preventative foot care and cardiovascular evaluation are also essential, with macrovascular disease a major problem for patients with long-term diabetes. Patients with type 1 diabetes have more severe progressive coronary artery atherosclerosis for any level of low-density lipoprotein cholesterol (50, 51). Neuropathy remains difficult to treat (52) despite the introduction of several newer medications.

Patients with diabetes and renal failure have a particularly poor prognosis when on dialysis. Every effort should be directed toward "early" renal transplantation in patients with type 1 diabetes and renal failure.

Conclusion

Type 1A diabetes has become perhaps the most intensively studied autoimmune illness, with progress in understanding genetic predisposition and prediction. There has been important progress in glucose monitoring and insulin therapy, with major improvement likely to result from the introduction of continuous glucose monitoring. A long-term goal is the development of effective therapy for the prevention of this predictable disorder. At present, meticulous monitoring and achieving clinical targets is essential to preserve health as these newer pathways enter clinical practice.

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Address all correspondence and requests for reprints to: George S. Eisenbarth, M.D., Ph.D., Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, Mail Stop B140, P.O. Box 6511, Aurora, Colorado 80045-6511. E-mail: george.eisenbarth@uchsc.edu.

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