The Prevention of Type I Diabetes Mellitus

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Despite continual advances in insulin therapy and monitoring technology, type I (insulin-dependent) diabetes mellitus in childhood remains a major problem, exacting a large physical and psychological toll on patients and their families. This results in large societal costs.

The prevalence of type I diabetes mellitus in the U.S. population younger than 40 years of age is approximately 1 in 300. If an individual has an affected first-degree relative, the risk of having type I diabetes mellitus is 1 in 20 (5%); if the father has type I diabetes mellitus, the child has a somewhat higher risk. The risk for the unaffected identical twin of a person with type I diabetes mellitus is 1 in 3. To prevent diabetes, the factors responsible for risk must first be identified.

NATURAL HISTORY

Clinically manifest type I diabetes mellitus follows a prodromal period of varying length, during which immunologic and metabolic abnormalities can be detected. Genetically predisposed individuals may be exposed to one or more environmental triggers of autoimmune destruction of β-cells, such as viruses or toxins. The autoimmune destruction causes the release of islet cell antigens, with the development of antibodies against these antigens. As β-cells are destroyed, patients lose the immediate insulin response (first phase) to intravenous glucose administration (Figure). Subsequently, abnormal oral glucose tolerance develops. A decline in insulin secretion has been noted as many as 10 or more years before the onset of clinical diabetes.

The long prodromal phase and the predictability of the disease have led to attempts to prevent or delay the onset of type I diabetes mellitus.

GENETICS

Susceptibility to type I diabetes mellitus is polygenic, with the major histocompatibility locus (human leukocyte antigen [HLA] region) having the greatest contribution. In type I diabetes mellitus, class II major histocompatibility complex alleles HLA-DR3 and HLA-DR4 were identified as susceptibility genes in the 1970s: 95% of Caucasians with type I diabetes mellitus were positive for DR3(DQB0201) or DR4(DQB0302) compared with 40% of the general population. HLA identical siblings of a proband with type I diabetes mellitus have a 1 in 7 risk for having the disease. If both DR3 and DR4 are shared, the risk increases to 1 in 4. The presence of DR2 and DR5 haplotypes has been associated with increased protection against the disease. HLA-DQB1 and HLA-DQA1 alleles have the greatest influence on susceptibility to type I diabetes mellitus. Certain combinations of these alleles increase the risk (DQB1*0302 and DQA1*0501), whereas others provide protection (DQB1*0602).

IMMUNologic Markers

Immunologic markers indicating ongoing β-cell destruction can often be detected long before...
Antigen-activated T-lymphocytes are T-helper cells that mediate both cellular and humoral immune responses. Two T-helper cell types are distinguished by their cytokine secretion patterns. T-helper 1 cells produce pro-inflammatory cytokines, such as interleukin-2 and interferon-γ, that regulate cell-mediated immunity. T-helper 2 cells produce anti-inflammatory cytokines (interleukin-4, interleukin-5, and interleukin-10) and are primarily responsible for the humoral immune response. Models of autoimmune diabetes in non-obese diabetic (NOD) mice and biobreeding rats have shown that autoreactive T-cells that mediate β-cell destruction belong to the T-helper 1 subset and the cytokines produced by T-helper 2 cells may prevent the autoreactive T-helper 1 cells from expressing inflammatory effects. Thus, type I diabetes mellitus may result from a disturbance in immunoregulatory circuits that leads to a dominance of T-helper 1 cells over T-helper 2 cells.

Oxygen free radicals and nitrous oxide may also cause β-cell injury. Nitrous oxide production has been demonstrated in pancreatic islets of biobreeding rats and NOD mice. In addition, islets have low levels of oxygen free radical scavengers.

**PREVENTION TRIALS**

The ability to predict the development of type I diabetes mellitus has led to efforts to prevent β-cell destruction in high-risk individuals. Major studies include avoidance of cow’s milk vaccinations, the European Nicotinamide Diabetes Intervention Trial (ENDIT), and the U.S. Diabetes Prevention Trials (DPT-1).

**Insulin**

Trials using insulin to prevent type I diabetes mellitus are based on the premise that insulin may act as an immune modulator, inducing immune tolerance, or that by putting the β-cells “at rest,” they will be less susceptible to immune attack. Administration of insulin prior to the development of diabetes may also decrease antigen expression.

Insulin given intranasally, orally, and subcutaneously to NOD mice has been shown to decrease the incidence of diabetes. Studies in newly diagnosed patients with type I diabetes mellitus indi-
cated that intensive insulin therapy for the first few days of treatment, using a device that frequently measures blood glucose and supplies insulin intravenously as needed, resulted in prolongation of the honeymoon phase with improved β-cell function and C-peptide production for more than a year.7,8

A large, multicenter trial, the DPT-1, is now under way and, it is hoped, will provide more answers as to whether insulin given to high-risk individuals (50% risk) before they have clinical type I diabetes mellitus can prevent or delay this disease. (For information about enrollment in this trial, call 1-800-425-8361.) In contrast to other interventions, insulin therapy is β-cell specific.

Nicotinamide

Nicotinamide is a water-soluble amide of nicotinic acid, and an oxygen free radical scavenger. In high doses it can prevent or delay disease in NOD mice. β-cells show increased resistance to β-cell toxic chemicals and inflammatory macrophages, and have increased regenerative capacities in the presence of nicotinamide.9,10

In humans, high doses of nicotinamide may exert some protective effect. A meta-analysis of 10 randomized, placebo-controlled trials in humans revealed better preservation of basal C-peptide secretion in the group treated with nicotinamide after 1 year.5 In a nonrandomized study of 22 nondiabetic but high-risk patients, 1 of 14 who chose treatment with nicotinamide developed type I diabetes mellitus, whereas all 8 of the patients who refused nicotinamide treatment developed type I diabetes mellitus.11 These results, promising data from the New Zealand population study,9 and the safety of nicotinamide led to the large ENDIT trial in 1994. This prospective, double-blind, placebo-controlled study has enrolled 600 ICA-positive, first-degree relatives of probands with type I diabetes mellitus from age 5 to 40 years. Patients have been randomized to receive either nicotinamide or placebo. Analysis is expected in 2002. A smaller German study did not show any protective effect.12

Cow's Milk

Several studies have suggested that cow's milk, introduced early into an infant's diet, may increase the risk of having type I diabetes mellitus by triggering the autoimmune process.13,14 Initial observations indicated an inverse relationship between type I diabetes mellitus and frequency of breastfeeding in Sweden and Norway. In 1994, a meta-analysis by Gerstein concluded that early exposure to cow's milk may increase the risk of type I diabetes mellitus by approximately 1.5-fold.14

Several mechanisms have been proposed. Antibodies to bovine serum albumin seem to have specific reactivity to the 17 amino acid peptide that has homology to a 69-kd protein from islet cells.13 These findings have, however, been disputed.8,13,14 Antibodies to β-lactoglobulin have been reported as independent risk factors for type I diabetes mellitus. A cellular response to β-casein has also been described in new-onset type I diabetes mellitus.13 The Trial to Reduce Insulin-Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR) study has been designed to determine whether the avoidance of cow's milk during the first 8 months of life reduces type I diabetes mellitus in children who are high-risk, first-degree relatives of probands with type I diabetes mellitus.15

Vaccines

Immunizations have been implicated in the pathogenesis of type I diabetes mellitus and proposed for its prevention. An increased incidence of type I diabetes mellitus in Finland was reportedly associated with institution of mandatory immunization practices against diphtheria—pertussis—tetanus, and more recent reports of an association between type I diabetes mellitus and Haemophilus influenzae vaccine have been cited to suggest that childhood immunizations may contribute to the development of type I diabetes mellitus. The timing of immunizations has also been associated with the rising incidence of the disease.16 An expert panel convened in 1998 by the National Institutes of Health found no evidence to support these claims.

More importantly, vaccines have been proposed as preventive agents. Insulin given intranasally, orally, and subcutaneously as an antigen to NOD mice decreases the incidence of diabetes. Antigen-based therapy with GAD 65
showed similar results. Pilot studies in humans are being considered.

**Neonatal Screening**

Because more than 90% of new cases of type I diabetes mellitus are diagnosed in those without a family history of disease, population-based screening and intervention will be needed to substantially reduce the incidence of this disease. Two strategies are possible. Primary screening for ICA followed by genetic and metabolic testing is the first. Initial screening for susceptibility genes followed by autoantibody and metabolic testing is the second. The former requires venous blood testing, rigorous standardization of assay techniques, adaptability of assays to mass population screening, decreased cost, and regular retesting. Alternatively, an advantage of screening for the diabetes susceptibility genes first is that HLA typing can be done on cord blood or filter paper spots at an early age (eg, newborns) and only patients with high-risk alleles would need to be tested further. Also, the initiation of the autoimmune cascade and the resulting molecular and cellular changes that occur in type I diabetes mellitus are thought to occur early in life. Therefore, studies done soon after birth will help us understand the immunopathogenesis of type I diabetes mellitus and the impact of environmental factors on initiating the autoimmune response.

Neonatal screening programs are being undertaken in Europe (Germany and Finland) and the United States (Denver, Colorado, and Florida). At the University of Florida in Gainesville, we are screening patients for the high-risk HLA alleles using dried blood spots on filter papers. Autoantibody testing for ICAs, GADs, IA2/ICA512, and IAAAs of those with higher risk profiles is done at 6 months of age and annually thereafter. Environmental factors, including infection, food intake, and immunization history, are assessed prospectively. Those identified at high risk of having type I diabetes mellitus will be considered for intervention.

**SUMMARY**

Now that prediction of type I diabetes mellitus has markedly improved, worldwide attempts to prevent the disease are under way (eg, DPT-1, ENDIT, and TRIGR). Subjects are being recruited and families of children or parents with diabetes should be informed about the availability of such studies and given the option to participate. The creation of a network of study sites or cooperative groups will allow for the implementation of new protocols aimed at preventing the disease. The greatest barrier to the prevention of diabetes is the lack of proven effective interventional agents. The journey toward prevention of type I diabetes mellitus has only just begun.

**REFERENCES**