Prevention of insulin-dependent diabetes mellitus: an overview of three trials

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SUMMARY Genetic, immune, and metabolic testing can reveal a person's risk of developing insulin-dependent diabetes mellitus (IDDM), and three large clinical trials are planned or underway to see if interventions can prevent IDDM in persons at risk.

KEY POINTS Researchers in diabetes prevention trials are screening first- and second-degree relatives of probands with IDDM for islet-cell antibodies. In the Cow's Milk Avoidance Trial, infant siblings of probands with IDDM will be randomized to receive either a baby formula containing a nonantigenic protein hydrolyzate or a standard cow's milk-based formula. The Diabetes Prevention Trial-Type I is randomly assigning subjects at high risk (more than a 50% probability of developing IDDM) to either receive insulin injections or undergo observation alone; subjects at intermediate risk (25% to 50%) will receive either oral insulin or placebo. In the European Nicotinamide Diabetes Intervention Trial, subjects receive either nicotinamide or placebo. If any of these trials show that IDDM can be prevented, then large-scale screening of children for IDDM risk factors may prove beneficial.

INDEX TERMS: INSULIN-DEPENDENT DIABETES MELLITUS; AUTOIMMUNITY, PREVENTION.
CLEVE CLIN J MED 1996; 63:270–274

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NOW THAT THE autoimmune process leading to type I or insulin-dependent diabetes mellitus (IDDM) is understood more clearly and a person's risk of developing it can be calculated more precisely, researchers are setting their sights on an exciting goal: preventing IDDM by intervening before it becomes clinically apparent. Three large-scale clinical trials—each testing a different intervention—are planned or already underway. Clinicians are eagerly awaiting the results, because success in any of these trials would have far-reaching implications. Specifically, if IDDM can be prevented, then large-scale screening might be justified to identify children who would benefit from preventive treatment.

THE SCOPE OF THE PROBLEM

Diabetes is by far the most common metabolic disease of childhood, with an annual incidence in the United States of 15 new cases per 100 000 persons younger than 18 years; approxi-

mately 1 child in 400 becomes diabetic by age 18. As high as this incidence is, it is even higher in Finland, where almost 1 in 200 children become diabetic before age 18—the highest incidence in the world.[1]

Purer insulin preparations, better insulin delivery systems, blood glucose monitoring, and the encouraging findings of the Diabetes Control and Complications Trial (in which stringent blood glucose control prevented diabetic complications) have led to better treatment. However, diabetes still imposes high rates of morbidity and premature mortality due to microvascular disease (retinopathy, nephropathy, neuropathy) and macrovascular disease (coronary artery disease, strokes, peripheral vascular disease).[2] The annual financial burden to the nation from all types of diabetes exceeds $100 billion in medical care and loss of productivity—more than 13% of the estimated $700 billion of total US health care expenditure.[3]

HOW IDDM DEVELOPS

IDDM results from an indolent autoimmune destruction of the pancreatic beta cells in genetically susceptible persons, usually beginning at a young age. The autoimmune disease process is most likely triggered by exposure to environmental factors in early childhood. A prodromal period (insulitis) of varying duration follows, during which immunologic and metabolic abnormalities can be detected long before the onset of clinical disease (*Figure*).[4–7]

In previous studies, patients with newly diagnosed IDDM who were given immunosuppressive drugs to try to halt further beta cell destruction and to allow residual beta cell recovery enjoyed remissions of only limited duration, suggesting that therapy had begun too late in the disease process. Consequently, investigators around the world are now concentrating on intervening earlier, ie, in persons at risk, those in the prodromal period, or early in pre-IDDM.

IDENTIFYING PERSONS AT RISK

Crucial to the design of any prevention trial is an accurate estimate of the risk of disease. Information about a person's level of risk will also be important if preventive interventions reach clinical practice. For example, a person at very high risk of becoming diabetic may accept a more-demanding therapy or even one with a risk of adverse events, if IDDM prevention can be reasonably assured. Persons with a relatively low risk may be more interested in treatments with minimal risk.

The likelihood that a person will develop IDDM (within 5 years) can be determined by assessing genetic, immune, and metabolic markers of islet autoimmunity.

Genetic susceptibility

Approximately 85% of patients with IDDM have no family history of the disease. However, siblings and offspring of probands with IDDM have a risk of developing IDDM of approximately 1 in 20, compared with about 1 in 300 in the general population. Consequently, the early-prevention trials have targeted this at-risk population.

The HLA-DR and DQ loci on the short arm of chromosome 6 provide the major genetic influence for developing IDDM. The serologically defined DR alleles 1, 3, 4, 8, and 16 convey susceptibility, while DR5 and DR15 (DR2) impart protection.[8] The DQA and DQB genes, which are in strong linkage disequilibrium, also powerfully influence the development of IDDM. DR3-associated DQA*0501/DQB*0201 and DR4-associated DQA*0301/DQB*0201 are the most common IDDM-prone haplotypes.[9,10]

Because the HLA susceptibility alleles are common in the general population, they have by themselves poor predictive ability. However, the presence of protective alleles (eg, the DR2-associated DQA*0102 and DQB*0602) makes IDDM unlikely, even among persons who have islet-cell antibodies (see below). Thus, such subjects were excluded from the Diabetes Prevention Trial-Type I (DPT-1).[11,12]

Immune markers

The presence of islet-cell antibodies in a nondiabetic relative of a diabetic patient imparts a disease risk of approximately 25%. However, when islet-cell antibodies are present in younger persons (siblings or children of affected parents), in a high titer (> 40 JDF (Juvenile Diabetes Foundation) units, or in association with DR3/4 heterozygosity, the risk increases to approximately 50%. Although insulin autoantibodies by themselves carry a very low risk for progression to disease, their presence in patients with islet-cell antibodies increases the 5-year risk to 50% to 70%.

Current prevention trials are using testing for islet-cell antibodies and insulin autoantibodies to

categorize subjects according to their risk of becoming diabetic. Ongoing studies suggest that measuring other additional autoantibodies, including those to glutamic acid decarboxylase (reported in up to 80% of relatives before diagnosis) and those to IA-2, a novel transmembrane tyrosine phosphatase target (reported in 50% to 60% of prediabetic subjects), may define risk even more precisely.[13]

Metabolic derangements

When serologic markers are considered together with metabolic changes, the precision of the prediction increases even further. In studies that helped to form the basis of the DPT-1 study, more than 50% of persons with persistent loss of the first-phase insulin response (during intravenous glucose tolerance testing), a sibling or parent with IDDM, and islet-cell antibodies (determined on two or more occasions) became diabetic within 5 years. (The first-phase insulin response is the immediate release of stored insulin from beta cells in response to a glucose load.) Persons with a normal first-phase insulin response, a diabetic relative, islet-cell antibodies, and insulin autoantibodies have a 25% to 50% risk, whereas if only islet-cell antibodies are present the risk is less than 25%. Changes in oral glucose tolerance occur late in the disease process, reflecting significant beta cell destruction and impending clinical disease.

PREVENTION TRIALS

The three major clinical trials aimed at preventing IDDM are the Cow's Milk Avoidance Trial, the Diabetes Prevention Trial-Type I (DPT-1), and the European Nicotinamide Diabetes Intervention Trial (ENDIT).

Cow's Milk Avoidance Trial

Background. An ideal strategy for preventing IDDM would be for genetically susceptible persons to avoid the environmental triggers of the disease. Epidemiologic studies have long implicated the early introduction of cow's milk in the pathogenesis of IDDM. A meta-analysis found that, overall, children who were given cow's milk before 3 months of age were 1.4 times more likely to become diabetic.[14] Further, a strain of nonobese diabetic (NOD) mice fed purified amino acid preparations instead of other sources of protein have a very low incidence of IDDM.[15] A pilot study to determine whether avoiding cow's milk in infants could prevent diabetes (the Trial to Reduce IDDM in the Genetically at Risk [TRIGR][16]) was started in Helsinki in 1992.

Study design. Prompted by the varied sources of supportive data, investigators in Europe and North America are planning a prospective, double-blind trial to determine whether avoiding cow's milk protein for at least the first 6 months of life will reduce the incidence of IDDM in the first 10 years of life. Some 10 000 newborn first-degree relatives of patients with IDDM will undergo an assessment of genetic risk by HLA typing. Those with protective or neutral genotypes will be excluded, leaving an estimated 5400 infants with high-risk genes for study.

Breast feeding will be encouraged for initial nutrition. When the mother wishes to wean the infant, subjects will receive either a standard cow's milk baby formula or one containing a nonantigenic protein hydrolyzate, until 6 months of age. The study, which has not yet begun recruiting subjects, will have a 90% power to detect a 33% difference in diabetes incidence between the two groups during the subjects' first 10 years of life.

The Diabetes Prevention Trial-Type I (DPT-1): insulin preventive therapy

Background. Once the autoimmune destruction of beta cells has begun, certain therapies might slow or stop it and thus delay or prevent the clinical onset of IDDM, if intervention occurs early enough. Some studies have shown that insulin administration may prevent IDDM, although the reasons for this are not understood. It is possible that insulin therapy allows beta cells to rest, diminishes production of beta-cell enzymes and proteins that act as target autoantigens, alters antigen presentation, or induces tolerance.

In studies in diabetic strains of rats and mice, daily subcutaneous insulin doses not only prevented diabetes but also markedly diminished the severity of the insulitis.[17,18] Oral insulin, given to nonobese diabetic mice, also delayed the onset of diabetes.[19] Similarly, in a number of animal models of autoimmune disease, as well as in patients with multiple sclerosis and rheumatoid arthritis, giving an oral antigen has been shown to reduce disease severity and cause few if any adverse effects.[20,21] Pilot studies in prediabetic relatives of probands with IDDM have been conducted in Boston and Gainesville,[22] and the large-scale DPT-1 is now under way to determine whether insulin treatment can prevent or delay the onset of IDDM in humans.

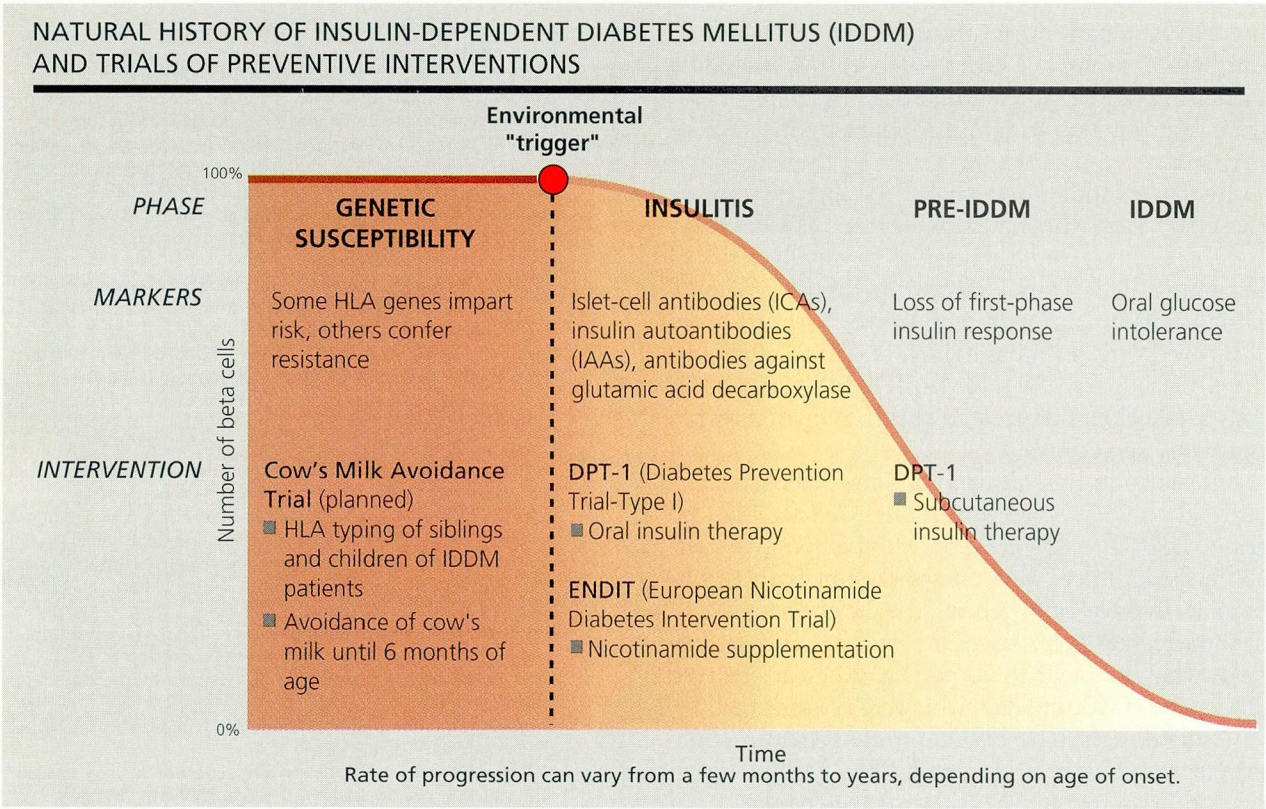

FIGURE. How insulin-dependent diabetes develops, and how early intervention might prevent or delay the clinical onset of disease. In genetically susceptible persons, exposure to an environmental trigger early in life initiates an autoimmune process that causes the number of beta cells to decrease. Three large-scale preventive trials, using different interventions, are planned or underway.

Study design. The DPT-1 investigators plan to test for islet-cell antibodies to screen approximately 60 000 first- and second-degree persons younger than 45 years of age who are relatives of probands with IDDM. Subjects with islet-cell antibodies then undergo further testing to confirm they have islet-cell antibodies, measure their insulin autoantibody level, establish if they have the HLA DQA*0102-B*0602 genes (an exclusion factor), and determine their first-phase insulin response by intravenous glucose tolerance testing.

These tests divide the subjects into a high-risk group (those having islet-cell antibodies and a low first-phase insulin response, who have more than a 50% chance of developing IDDM within 5 years) and an intermediate-risk group (those with islet-cell antibodies and insulin autoantibodies but a normal first-phase insulin response, who have a 5-year risk of developing IDDM of 25% to 50%). High-risk subjects are being randomized either to receive twice-daily subcutaneous injections of ultralente insulin, supplemented annually with 5-day intravenous insulin infusions, or to undergo observation only. Intermediate-risk subjects will be randomized to receive either oral insulin or placebo.

The DPT-1 will require 340 high-risk subjects and 490 intermediate-risk subjects to detect a 35% decrease in IDDM over a 5-year period with a statistical power of 80%.

How to refer patients. There will be more than 200 centers participating in the study. Physicians who wish to refer first- and second-degree relatives of patients with IDDM to a DPT-1 trial site for islet-cell antibody screening can call 1-800-633-2122 for further information and the location of the nearest participating center.

European Nicotinamide Diabetes Intervention Trial (ENDIT)

Background. Nicotinamide, an antioxidant, is believed to protect against diabetes by preventing nicotinamide-adenine dinucleotide depletion dur-

ing DNA repair by inhibiting poly (ADP)ribose synthetase. However, other mechanisms, including inhibition of free radical formation, B-cell regeneration, or protection from macrophage toxins, may be involved.[23]

In a nonrandomized trial, 14 subjects younger than 16 years who had first-degree relatives with IDDM and who were themselves at very high risk of becoming diabetic took daily doses of nicotinamide (150 to 300 mg/year of age, up to 3 g) and were compared with a similar cohort of 8 untreated children. During 2 to 30 months, IDDM developed in only 1 nicotinamide-treated child, compared with 6 untreated subjects.[24]

In a study in New Zealand of some 80 000 5- to-7-year-old children, 20 000 were screened for islet-cell antibodies.[21] The 150 children who had positive islet-cell antibody titers were offered therapy with nicotinamide. In preliminary reports, the incidence of IDDM in the screened group was near 8 per 100 000/year, well below the rate of 15 to 20 per 100 000/year observed among the 60 000 children who were not screened.

Study design. The ENDIT study began in 1993, primarily in Europe and Canada. The ENDIT investigators are screening 40 000 first-degree relatives of IDDM patients, aged 5 to 40 years. They estimate that more than 400 subjects will have islet-cell antibodies and will be randomized to receive either nicotinamide or placebo. With an expected rate of progression to IDDM of 40% in the placebo group, the proposed 5-year observation period will allow a 90% power to observe a 35% reduction in the incidence of IDDM.

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