In Pursuit of Type 1 Diabetes Prevention

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STUDY

Diabetes Prevention Trial–Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002.

SUMMARY

Objective. To determine whether insulin can prevent or delay the onset of overt type 1 diabetes in relatives of patients with type 1 diabetes who are at increased risk of the disease.

Design and methods. The Diabetes Prevention Trial–Type 1 (DPT-1) was a randomized, controlled, open comparison trial of prophylactic intervention with parenteral insulin versus no treatment in prediabetic subjects. First- and second-degree relatives of type 1 diabetic patients were recruited and screened with a test for islet cell antibodies (ICAs). Those who tested positive for ICAs were then staged to define their risk for diabetes by measuring insulin autoantibodies (IAAs), assessing oral glucose tolerance, and measuring first-phase insulin response to intravenous glucose.

Researchers also screened for the presence of the haplotype known to be protective against diabetes (HLA-DQA1*0102, DQB1*0602). Its presence excluded individuals from further participation.

ICA-positive relatives were eligible for the parenteral trial if their first-phase insulin response was below a set threshold, if their oral glucose tolerance test (OGTT) results were not completely normal, or both. Such individuals have a 5-year projected risk of diabetes of more than 50%. Relatives who tested positive for ICAs and IAAs with normal glucose tolerance and a first-phase insulin response above the set threshold have intermediate risk for diabetes (5-year projected risk of 25–50%). These individuals were offered enrollment in the oral insulin trial, which is ongoing.

The high-risk subjects were randomly assigned to either the experimental intervention (parenteral insulin) or to a control group receiving no intervention. The control group was closely monitored and underwent the same schedule of testing throughout the study as the experimental intervention group.

Subjects in the intervention group received parenteral insulin in the form of twice-daily subcutaneous insulin injections, plus annual 4-day intravenous insulin infusions, for which they were admitted to a hospital research unit. All insulin doses were calculated according to weight (0.125 units/kg subcutaneously, 0.015 units/hour intravenously) and adjusted with changes in weight or in response to hypoglycemia. Assessments included an OGTT every 6 months and either an intravenous glucose tolerance test or a mixed-meal tolerance test every year.

Results. More than 89,800 relatives were screened during the nearly 7-year study. After staging, 339 were eligible and underwent randomization, 169 to intervention and 170 to close observation. A total of 354 were excluded before randomization because they had an initial OGTT consistent with the diagnosis of diabetes.

Subjects were followed for a median of 1,345 days (3.7 years). Diabetes was diagnosed in 139 participants: 69 in the intervention group and 70 in the observation group. The majority in whom diabetes developed were asymptomatic (73.4%). The rate of progression to diabetes was higher in the subjects who had baseline OGTTs that were abnormal (22 vs. 10% per year). β-Cell function (as indicated by C-peptide level in response to the tolerance tests) before the diagnosis of diabetes was not different between the two groups. There were no episodes of severe hypoglycemia during the study.

Conclusion. In the DPT-1, in high-risk relatives of patients with type 1 diabetes selected by the criteria described, the parenteral insulin regimen utilized did not delay or prevent the development of diabetes.

COMMENTARY

Researchers have speculated for decades about whether insulin given before onset of clinical disease could alter the progressive destruction of β-cells that results in a decline in, and eventual complete loss of, insulin production by the pancreas. In several animal models, diabetes has been prevented by insulin injections given before onset of hyperglycemia.[1–6] While such an intervention would appear attractive to test in humans, it was not feasible until reliable methods of predicting diabetes risk based on genetic, autoimmune, and metabolic factors were available.

Small pilot studies in humans were completed, and their results suggested that insulin treatment could delay diabetes in high-risk individuals.[7–9] The results of these pilot studies were so per-

suasive that some physicians began to advise their diabetic patients' high-risk relatives to take insulin.

Families anxious for a cure began to request such treatment. To many, giving insulin seemed a logical thing to do, not only based on these pilot studies, but also on an earlier study of new-onset diabetic patients demonstrating preservation of C-peptide production and easier achievement of good glycemic control when insulin treatment was given aggressively from the time of diagnosis.[10,11] If insulin "spares" β-cell function when given soon *after* the onset of disease, why wouldn't it work to *delay or prevent* the onset?

It was believed that exogenous insulin might accomplish this by one of two mechanisms. Because evidence suggests that only an actively secreting β-cell is susceptible to immunological attack, giving exogenous insulin might allow β-cells to "rest," thus protecting them from destruction. Alternatively, insulin might act as an antigen that could potentially interfere with immunologically mediated β-cell destruction. Such were the hypotheses that spawned the DPT-1.

Unfortunately, the results of the parenteral trial demonstrated that insulin, in the manner given, did not delay or prevent the onset of clinical disease in these relatives at high risk. This outcome was understandably disappointing to many who were involved in this long, labor-intensive trial, including researchers, volunteer participants, and the wider medical community.

However, valuable information is being acquired from the DPT-1 results. The trial is yielding knowledge about what characterizes diabetes risk and more information about the natural history of diabetes development, for example. The trial also demonstrated convincingly that diabetes could be predicted with accuracy using the tools described. Additionally, the long-held belief that type 1 diabetes was a disease of acute onset has been completely refuted. Almost three-fourths of the subjects in the study were asymptomatic when diabetes was diagnosed, a result of the close monitoring of all identified high-risk individuals.

Future follow-up of study participants may further refine our knowledge of diabetes development and improve predictive tools to facilitate the planning of future intervention trials. High-risk subjects who did not develop diabetes remain at high risk. They need to be vigilant for the onset of signs and symptoms of diabetes and to stay in contact with their own physicians.

Why the intervention demonstrated no benefit when the pilot studies seemed so promising is not known. One consideration is that the doses of subcutaneous insulin given in this study, limited to avoid hypoglycemia, may have been too small to "rest" the β-cells and protect them from attack. It is also possible that high-risk DPT-1 participants had disease progression that was too far advanced for such an intervention to be effective. Intervention at an earlier stage, such as is being studied in the ongoing oral insulin trial, may prove more effective. Additionally, the oral route of insulin delivery may be more likely to modify the immunological environment in the islets in such a way as to stop or slow the progression of β-cell destruction.

Despite the results, significant lessons can be learned from the DPT-1. Crucial among these is the lesson about the practice of adopting unproven treatments into clinical care based on unproven theories and the results of animal studies and human pilot studies. The results of the DPT-1 are distinctly disparate from the early pilot studies, a compelling demonstration that clinical practice should not be altered on the basis of outcomes from anything less than large, randomized trials.

The best medicine is evidence-based medicine. Prophylactic interventions for disease prevention should only be adopted when there is real proof of efficacy. Thus, we move onward in the pursuit of type 1 diabetes prevention.

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