EDITORIAL



# Toward Primary Prevention of Type 1 Diabetes

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**The incidence of type 1 diabetes** has been progressively increasing during the past several decades, particularly among children younger than 5 years.[1] At the same time, there has been substantial progress in understanding the pathogenesis of the disease and identifying those at risk of progressing to type 1 diabetes.[2] In children at genetic risk, diabetes-related autoantibodies appear, followed by the evolution of metabolic abnormalities and the eventual clinical appearance of the disease.[2] If individuals identified by genetic markers subsequently undergo seroconversion and develop 2 or more diabetes-related autoantibodies, their risk of progression to type 1 diabetes is 75% over 10 years and appears to be almost inevitable over 20 years.[3] However, attempts at both primary prevention, ie, before seroconversion, and secondary prevention, ie, in those with diabetes-related autoantibodies, have not been successful.[4] The interventions evaluated to date have been limited to those deemed extremely safe, because such interventions would be used in at-risk individuals who may or may not actually progress to type 1 diabetes.

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One hope has been that therapy with a diabetes-related antigen, administered in a manner that favors immune regulation rather than immune aggression (activation of effector T lymphocytes directed against beta cells), could achieve protection without compromising general immune response—basically antigen-based vaccination. One way of approaching antigen-specific immunotherapy is to leverage the concept of mucosal tolerance, in which antigen presented across a mucosal barrier preferentially induces a regulatory immune response. In type 1 diabetes, mucosal tolerance has been exploited in secondary prevention studies using nasal insulin[5,6] and in secondary prevention and recent-onset type 1 diabetes studies using oral insulin. However, these studies have not been successful in altering the course of the disease.

Yet in the Diabetes Prevention Trial–Type 1 (DPT-1) oral insulin trial, a study of oral insulin in secondary prevention, a subgroup with high levels of insulin autoantibodies at baseline had a projected 4.5- to 5-year delay in the development of clinical type 1 diabetes.[7] A subsequent analysis showed continued beneficial effects in the subgroup, even after oral insulin was discontinued.[8] Because the subgroup was identified in a post hoc analysis and the findings therefore could only be considered hypothesis-generating, an ongoing trial is examining oral insulin in participants similar to those in the subgroup with high-titer insulin autoantibodies.

Participants in the intervention group of the DPT-1 oral insulin trial received 7.5 mg of oral insulin daily.[7] The choice of dose was somewhat arbitrary, as previous studies of oral insulin had only been conducted in rodent models of type 1 diabetes. These animal studies had shown profound beneficial effects.[9]

At the same time as the DPT-1 trial, 3 studies with oral insulin were conducted in patients with recent-onset type 1 diabetes.[10-12] These studies used various doses of oral insulin daily, ranging from 1 mg to 10 mg. The studies did not demonstrate an effect on beta cell function, except for one analysis that showed retention of endogenous beta cell function at a dose of 1 mg, but the response was dependent on initial stimulated C-peptide response, age at diabetes onset, and numbers of specific islet cell autoantibodies.[12] The complex analysis did not permit a clear conclusion to be drawn. The contrast between results in rodent models and those in humans has led to considerable debate as to appropriate dose, dosing schedule, need for an adjuvant, eligibility criteria, and stage of the disease to evaluate oral insulin.

With this background, the Pre-POINT Study Group conducted a pilot dose-ranging study, reported in this issue of *JAMA*, to determine the immunologic effects of oral insulin given to children aged 2 to 7 years who had relatives with type 1 diabetes and who were at extremely high genetic risk for type 1 diabetes but did not have evidence of diabetes autoantibodies.[13] The study was small, with only 15 children receiving oral insulin and 10 children receiving placebo. No adverse effects, signs of allergy to oral insulin, insulin-related adverse events, or evidence that oral insulin induced type 1 diabetes in genetically at-risk children were found. However, daily oral administration of 67.5 mg of insulin actively engaged the immune system, with features of immune regulation in 5 of 6 children (83.3%) receiving this dose,[13] a much higher dose than that used in the earlier clinical trials. It is clear from previous studies that the dose of insulin is critically important, and this study informs future research efforts.

Previous studies with oral insulin used metabolic outcome measures, such as C-peptide preservation, as an index of beta-cell function,[10-12] or appearance of clinical type 1 diabetes.[7] In contrast, the Pre-POINT study used extensive contemporary methods for assessing immune response and demonstrated findings consistent with the concept that oral exposure to insulin can promote a protective regulatory T-cell response.[13]

A definitive study based on the Pre-POINT Study would be a primary prevention study involving relatives without diabetes autoantibodies but with genetic risk. The Pre-POINT Study was limited to individuals with the highest genetic risk, principally those with HLA haplotypes HLA DR4-DQB1*0302 or DR4-DQB1*0304. Others with risk not quite as high would likely be included in a definitive study. Two previous clinical trials have used a broader HLA definition for potential entry.[6,14] A ques-

tion that will need to be addressed in a definitive trial is whether to screen for genetic risk only those newborns with a relative who has type 1 diabetes, as was done in one primary prevention study,[14] or to screen for genetic risk in the entire population of newborns, as was done in another study in which at-risk individuals were followed up until antibodies appeared and then offered enrollment in a secondary prevention study.[6]

Another issue is age. In the Pre-POINT study, eligible children were 2 to 7 years old. Yet the peak incidence of islet autoantibodies occurs between 6 months and 2 years.[15] It is possible that the study included a survivor cohort that was antibody-negative because the participants had already passed the period of likely seroconversion. Consequently, to avoid missing enrollment prior to seroconversion, a definitive trial would need to enroll individuals younger than 1 year. Including younger children would complicate administration of the study medication, and additional questions of safety may arise.

A number of other promising approaches are under investigation. One potential therapy for primary prevention is the use of a vaccine consisting of a cocktail of several peptides derived from the proinsulin molecule. Phase 2 trials with such a cocktail are expected to begin in 2016.

Another intriguing approach is a strategy for tolerance restoration using mucosal delivery of biologically engineered *Lactococcus lactis* genetically modified to secrete an autoantigen (eg, proinsulin or glutamic acid decarboxylase) along with the immunomodulatory cytokine IL-10 in a setting where the patient has been treated systemically with low-dose anti-CD3 monoclonal antibody.[16]

In addition, methyldopa has been found to block communication between antigen-presenting cells and naive T-lymphocytes when insulin is the antigen being presented. Thus, methyldopa has the potential to slow the destruction of insulin-producing cells. Because methyldopa is an approved therapeutic agent and is of sufficient safety that it is used during pregnancy, this strategy, currently being examined in pilot studies, holds promise.

It is now possible to identify children at increased risk for type 1 diabetes at birth, and there is an identifiable sequence of events that culminates in impaired insulin secretion and overt type 1 diabetes. What is missing are interventions to arrest this process prior to irreversible damage to the pancreatic beta cell. The promise of autoantigen-specific therapy for prevention of type 1 diabetes in humans has yet to be realized. The Pre-POINT study provides additional evidence to inform trial design and increases enthusiasm for cautiously moving forward with a study of primary prevention in genetically screened children.

## ARTICLE INFORMATION

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