

# Prevention Opportunities of Type 1 Diabetes in Children

## Abstract

Type 1 diabetes results from autoimmune destruction of insulin-producing  $\beta$  cells in the pancreas. Genetic and environmental factors act together to precipitate the disease. The excess mortality associated with the complications of type 1 diabetes and the increasing incidence of childhood type 1 diabetes emphasize the importance of therapeutic strategies to prevent this chronic disorder. In the past 20 years, multiple clinical trials have attempted to find prevention approaches for type 1 diabetes in children before its occurrence (primary prevention), during the initial stage of autoimmune development (secondary prevention), or even after diagnosis of diabetes (tertiary prevention).

**Keywords:** Type 1 diabetes prevention;  $\beta$ -cell function; Immunomodulators; Immunotherapy; Antigen-specific vaccines; Monoclonal antibodies

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Review Article

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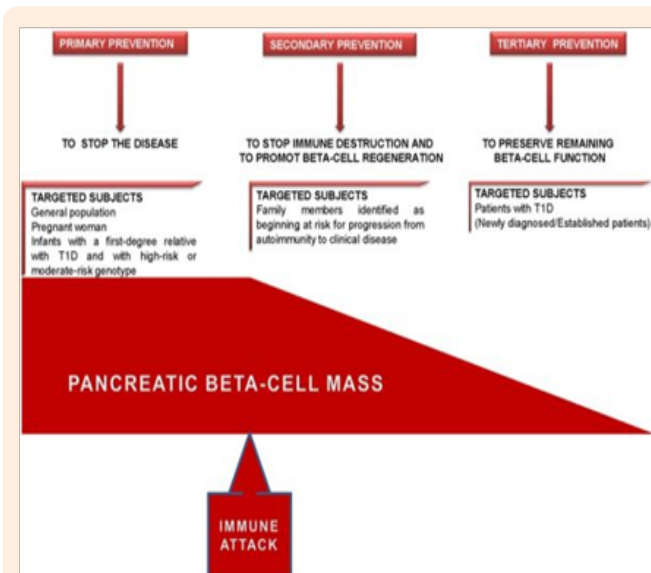
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**Abbreviations:** T1DM: Type 1 Diabetes Mellitus; GAD: Glutamic Acid Decarboxylase; IA-2: Insulinoma-Associated Protein 2; Znt8: Zinc Transporter; BCG: Bacille Calmette–Guerin; IL-1: Interleukin-1

## Introduction

The main stages in the development of type 1 diabetes and prevention approaches are summarized in Figure 1. The initial step-development of islet autoimmunity marked by the presence of auto antibodies to insulin, GAD, IA-2, and tyrosine phosphatase or Znt8-is believed to be driven by environmental trigger(s) [1]. Over the past 40 years, the incidence of childhood type1 diabetes worldwide has increased by 3–5% annually [2].



**Figure 1:** Stages of the development of type 1 diabetes and prevention opportunities at each stage.

Elimination of the environmental trigger (s) responsible for this epidemic would be the most efficient approach to primary prevention. After initiation of islet autoimmunity, most patients have a long preclinical period that offers opportunity for secondary prevention-halting progression to clinical diabetes. Restoration of insulin secretion after diagnosis of diabetes constitutes the tertiary prevention. I can summarize the current approaches to prevent type 1 diabetes with these measures [3]:

- Avoidance of environmental triggers of islet autoimmunity such as cow's milk or gluten, as well as supplementation with nutrients for which deficiency presumably promotes islet autoimmunity, e.g. n-3 fatty acids or vitamin D.
- Antigen-specific "vaccination" using islet auto antigens, e.g., intact insulin, altered insulin or proinsulin peptides, GAD65.
- Non-antigen-specific systemic therapies that range from mild modulation with oral nicotinamide or BCG vaccination [4] to immuno suppression and cellular therapies.
- Stimulation of  $\beta$ -cell regeneration in conjunction with suppression of apoptosis that is increased in islet autoimmunity to overcome the relapsing-remitting course of pre-diabetes.
- Metabolic modifications, such as weight loss, increased physical activity, and  $\beta$ -cell rest [4-6].

## Primary Prevention of T1DM

The target population for primary prevention trials is young children who carry high-risk HLA-DR, DQ genotypes, especially in children of first-degree relatives. Ongoing primary prevention trials include largely low-risk dietary modifications: elimination of cow's milk [7] or gluten [8] and supplementation of diet with n-3 fatty acids [9] or vitamin D [10].

## Role of cow's milk

The cow's milk hypothesis is being tested by the Trial to

Reduce type 1 diabetes in the Genetically at Risk (TRIGR) [7]. This randomized, double-masked trial is evaluating the effect of hydrolyzed infant formula, where protein fragments are too small to stimulate the immune system, compared with cow's milk-based formula. Eligible to participate were newborns who had a first-degree relative with type 1 diabetes and one of the high-risk HLA-DQ genotypes. The recruitment of 2,160 children from 77 centers in 15 countries was completed at the end of 2006. All participant mothers received the recommendation to breast-feed for at least the first 6 months of life. If a mother was unable to exclusively breast-feed before the baby was 8 months of age, her child was randomly assigned to either a formula of extensively hydrolyzed protein (Nutramigen) or a formula based on non hydrolyzed cow's milk (Enfamil) containing a small amount of Nutramigen (for masking purpose). The main end point of the trial is development of diabetes by the age of 10 years [7].

### Role of gluten

BABY DIET study is evaluating the effect of delaying exposure to gluten until the age of 1 year [8].

### Role of docosahexaenoic acid

The study of Norris et al has enrolled pregnant women in their 3rd trimester expecting high-risk babies based on family history and newborn first-degree relatives with high-risk HLA-DR, D Q genotypes. It has proved that dietary intake of omega-3 fatty acids by pregnant women and newborn babies before 6 months of age could be associated with reduced risk of type 1 diabetes in children at increased genetic risk [9]. The Trial Net Nutritional Intervention to prevent type I diabetes (NIP) is a pilot study that enrolled pregnant women in their 3rd trimester expecting high-risk babies based on family history and newborn babies as in Norris' study [11].

### Role of vitamin D

Vitamin D supplementation in early childhood has

attracted attention as a possible primary preventive measure [12]. However, this interest has been mitigated by potential nephrotoxicity of vitamin D. At least one phase I clinical trial is testing the feasibility of this approach [10].

### Secondary Prevention of T1DM

Approximately 1 in 20 first-degree relatives and 1 in 300 people without type 1 diabetes in the immediate family have multiple islet auto antibodies. Most young individuals with multiple islet autoantibody positivity progress to diabetes in 5-10 years; however, the rate of progression decreases with age. Four large secondary prevention trials have found no effect on the rate of progression to clinical type 1 diabetes for insulin administered parenterally [13], orally [14], or intranasally [15], as well as for oral nicotinamide [16]. Two large randomized double-masked secondary prevention trials using oral and intranasal insulin are still underway [17,18]. In the DPT-1 trial of oral insulin, the median duration of follow-up was 4.3 years; 97 subjects developed T1D - 44 in the oral insulin group and 53 in the placebo group, as summarized in Figure 2. The average proportion of subjects who progressed to diabetes was 6.4% per year in the oral insulin group and 8.2% per year in the placebo group, meaning that oral insulin did not prevent or delay development of T1D [14].

This observation led to a second oral insulin trial, conducted by the Type 1 Diabetes Trial Net consortium. The study is enrolling first-degree relative's age 1-45 years and second-degree relative's age 1-20 years (the relative with diabetes must have been diagnosed before the age of 40 years and started on insulin within the 1st year of diagnosis). Eligible subjects must be positive for insulin auto antibodies on two samples within a 6-month period and meet additional criteria for other islet auto antibodies [19]. Thus far, the secondary prevention trials have failed to prevent or delay the onset of diabetes. In the near future, we will likely see a resurgence of other secondary prevention trials translating the most successful findings from tertiary prevention trials in patients with established type 1 diabetes.

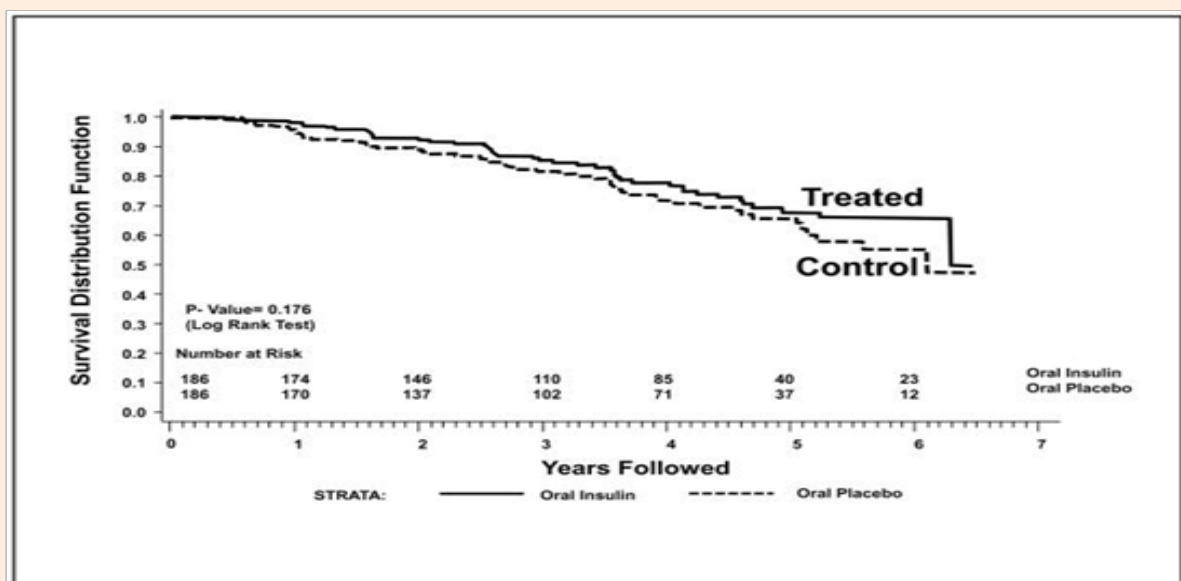


Figure 2: Life-table depicting time to diagnosis of type 1 diabetes in the DPT-1 oral insulin trial.

## Tertiary Prevention of T1DM

In the past several years, trials in patients with newly diagnosed type 1 diabetes became the main focus of the research community, as it is easier to recruit participants after diagnosis of diabetes. The goal of tertiary prevention is preservation of remaining islet  $\beta$ -cells to induce and prolong (partial) remission. Actually a spontaneous temporary remission from insulin dependency may occur in up to 27% of patients, soon after diagnosis, and may be related to  $\beta$ -cell rest caused by insulin treatment [20]. A realistic outcome of tertiary prevention trials is prolongation of residual insulin secretion, rather than complete reversal of diabetes.

### Antigen-specific vaccines

In the past several years, perhaps the most exciting development in the area of tolerance induction has been apparent efficacy of Diamyd vaccine based on the whole recombinant human GAD65 (rhGAD65) molecule suspended in alum. Clinical trials in late-onset autoimmune diabetes in adults (LADA) and adolescents with newly diagnosed type 1 diabetes [21,22] have suggested benefit.

Diamyd showed some promise of efficacy in Phase 2 clinical testing but then failed to meet its primary efficacy endpoint (preservation of beta cell function) in a follow on Phase 3 study [23]. DiAPREV-IT, an investigator-initiated Phase II study of Diamyd in 50 children at risk of T1D is ongoing with results expected in 2015 [24]. The Diabetes Vaccine Development Centre is funding a long running study in Melbourne, Australia of nasal insulin for T1D prevention in autoantibody positive first-degree relatives, but with slow recruitment the study may never reach its recruitment target [25].

Interleukin-1 $\beta$  (IL-1 $\beta$ ), a pro-inflammatory cytokine produced by  $\beta$ -cells or macrophages, represents a potential therapeutic target in diabetes. Anti-IL-1 $\beta$  antibody alone or combined with GAD65 vaccine could reverse diabetes development in a virus-induced mouse model. Given alone, anti-IL-1 $\beta$  had no effect on diabetes, while GAD65 plasmid resulted in 33% disease reversal after a 5-week observation. Despite unsuccessful clinical trials using anti-IL-1 $\beta$  mono therapy, promise for treatment of type 1 diabetic patients with IL-1 $\beta$  blockade combined with antigen-specific vaccines is still available [26].

### Systemic immuno modulators

Numerous non-antigen-specific immuno modulators have been tried in newly diagnosed patients. In early 2007, an excellent review by Staeva-Vieira et al. [27] summarized previously completed interventions, now largely of historical value. Some interventions, e.g., cyclosporine A, azathioprine, and anti-thymocyte globulin (ATG) plus prednisolone, had unattractive side effects, including weakening of immunity to infections, renal and pancreatic toxicity, and potential long-term risk of malignancies.

Cyclosporine A was efficacious in prolonging insulin production; however, the treatment had to be continued for at least 6–12 months to show benefit, and the effect was lost when the drug was discontinued. In addition, the patients would

progress to insulin dependency within 3 years, even if treatment was continued and C-peptide secretion was maintained. Nevertheless, cyclosporine trials provided a proof of principle that immuno suppression can slow the destruction of the  $\beta$ -cells, even if it cannot stop it [28].

Azathioprine is an immunosuppressive drug that inhibits or prevents T-cell responses to antigen. In this old double-blind study of 46 patients treated with azathioprine and glucocorticoids, insulin could be discontinued in 10 of 20 treated patients, as compared with 2 of 20 patients in the placebo group. Endogenous insulin secretion (measured as the plasma C-peptide response to a liquid meal) also improved. However, only three treated patients remained in remission at one year [29].

A phase I clinical trial has confirmed that the use of a BCG vaccine to raise levels of an immune system modulator can cause the death of autoimmune cells targeting the insulin-secreting cells of the pancreas and temporarily restore insulin secretion in human patients with type 1 diabetes. Results of the study led by Denise Faustman are being published in the open-access journal PLoS ONE, and a larger Phase II trial is currently underway [30].

### Immunotherapy with Monoclonal antibodies

Immunotherapy trials in recent-onset type 1 diabetes had mixed results, with some therapies-anti-CD3 monoclonal antibodies targeting T cells, anti-CD20 monoclonal antibodies targeting B cells [31]-showing promise, with at least transient improvement in  $\beta$ -cell function compared with randomized control groups.

**Teplizumab:** This monoclonal anti-CD3 antibody has received a lot of attention, and it is considered the most extensively studied immunological approach to T1D. A short course of anti-CD3 (six to fourteen days) early in the course of the disease has the potential to profoundly alter the course of the disease for many years. When used in adequate doses anti-CD3 consistently has been shown to preserve C-peptide [32,33]. In the current issue, Herold et al. [32] report the results of the Autoimmunity-Blocking Antibody for Tolerance in Recently Diagnosed Type 1 Diabetes (AbATE) trial which has demonstrated that in responders the mean preservation of C-peptide continues at baseline levels for 2 years [34].

Protégé trial, a randomized double-blind, parallel placebo-controlled two year study of three intravenous teplizumab dosing regimens, administered daily for 14 days at baseline and again after 26 weeks, in new-onset type 1 diabetes. Of 516 randomized patients, 513 were treated, and 462 completed 2 years of follow-up. Teplizumab (14-day full-dose) reduced the loss of C-peptide at 2 years versus placebo. Exogenous insulin needs tended to be reduced versus placebo. No new safety or tolerability issues were observed during the second year [35].

**Rituximab:** Rituximab is a monoclonal antibody that targets the CD20 receptor unique to B-cells inhibiting its function, thus reducing presentation of auto antigen to T-cells and theoretically secondarily preventing B-cell expansion and islet autoantibody production. This medication is approved for the treatment of non-Hodgkin's lymphoma and has shown success in treatment

of patients with rheumatoid arthritis. Trial Net has completed a phase II trial including 4 weekly injections of rituximab, and the results were presented at the American Diabetes Association's Scientific Sessions in June 2009. Newly diagnosed patients with type 1 diabetes (age 8–40 years) treated with rituximab had higher C-peptide after a mixed meal and lower A1C and insulin doses compared with the placebo group [31].

### Immuno suppression with MMF

Mycophenolate mofetil (MMF, Cellcept) inhibits proliferation of both T- and B-lymphocytes. In a multicenter randomized trial, 126 patients with type 1 diabetes for less than three months were randomly assigned to MMF, MMF plus daclizumab (an anti-IL-2 receptor monoclonal antibody that selectively binds the IL-2 receptor, inhibiting IL-2 mediated T-lymphocyte proliferation) or placebo. After two years, there was no significant difference in the mean area under the curve for C-peptide levels during a mixed-meal tolerance test. Thus, neither MMF alone or in combination with daclizumab slowed progression of beta-cell destruction in recently diagnosed type 1 diabetes [36,37].

### Metabolic control and $\beta$ -cell rest

Weight loss and increased physical activity can neutralize the powerful effect of insulin resistance on progression to type 1 diabetes [4]. Meticulous blood glucose control after diabetes onset resulting in  $\beta$ -cell rest is also believed to help preserve residual insulin secretion [5] and the Trial Net Metabolic Control Trial is about to test this hypothesis [6].

### Conclusions and a Look Into The Future

Genetic and environmental factors that determine the relapsing-remitting course of  $\beta$ -cell destruction, culminating in full insulin dependence, are being discovered. In the long run, primary prevention of islet autoimmunity will likely be the optimal approach to the prevention of type 1 diabetes, especially in high-risk groups, such as first-degree relatives. However, environmental triggers of islet autoimmunity need to be better defined. If a primary prevention is not feasible in the general population, mass screening for islet auto antibodies and secondary prevention may be the next option. As patients develop autoimmunity,  $\beta$ -cell function declines and so does the potential therapeutic benefit of intervention. Tertiary prevention trials of type 1 diabetes in children seem to be more promising, as it is easier to recruit participants after diagnosis of diabetes. But using antibody agents is still relatively nonspecific and potentially toxic to some trial participants. Type 1 diabetes prevention research is expanding at an unprecedented rate, and prevention opportunities will have a bright future protecting our lovely children from this progressive epidemic.

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