Evaluation of Preventive Studies in Type 1 Diabetes Mellitus
Tip 1 Diabetes Mellitusta Önleme Çalışmalarının Değerlendirilmesi

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Abstract
Type 1 diabetes mellitus (DM) is a chronic autoimmune disease in which destruction of the beta cells in the islets of Langerhans results in insulin deficiency and hyperglycemia. We only definitely know that autoimmunity is the most important effector mechanism of type 1 DM. Type 1 DM precipitates in genetically susceptible individuals after an exposure to environmental trigger. According to current data, type 1 DM-associated genes are classified as susceptibility and protective genes. This insidious disease process evolves over a period of years. Prevention of type 1 DM requires detection of the earliest events in the process. Until now, autoantibodies are generally used as a serum biomarker, but current studies about T cell and metabolome might strengthen diagnostic view. Current preventive clinical studies usually focus on environmental factors. During the natural course of type 1 DM, many strategies have been tested at different stages in the form of primary, secondary and tertiary studies. The aim of the intervention studies for type 1 diabetes is to suppress pathogenic autoreactivity, restore/preserve beta cell mass and function to sufficient levels to provide good metabolic control, and to delay or prevent disease development. Therapeutic studies evaluate the effect of antigen specific and non-specific immune interventions, restoration of the damaged beta cells and also combination of these therapies. The results of intervention studies done till now are modulation of autoimmune process and partial prevention of loss of insulin release following the diagnosis. A single long-term effective prevention has not been identified yet. Turk Jem 2013; 17: 38-45

Key words: Type 1 diabetes mellitus, autoantibody, preventive studies

Özet

Anahtar kelimeler: Tip 1 diabetes mellitus, otoantikor, önleme çalışmaları

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**Introduction**

**Pathogenesis**
We need to know the stage of the disease to stop and prevent the process of Type 1 Diabetes. Type 1 DM can occur as a result of extensive immune dysregulation like IPEX or APS1 syndromes and respectively it can occur as a result of mutations in FOXP3 (forkhead box P3) and the autoimmune regulator gene (AIRE) (1,2). However, the majority of patients with autoimmune diabetes does not have severely impaired immunity. Most cases have two characteristics: at least one HLA class II haplotypes and islet autoantibodies. Therefore, independent from etiologic factor or factors, the development of islet autoimmunity may occur. The start of the disease progress is the effector immune response of the islet beta cell antigens. The first detectable finding of this process is the appearance of islet autoantibodies (3).

Islet autoantibodies rarely appear in the first 6 months. In children with a family history the peak incidence is reached around the age of 1-2. At first insulin antibodies or antibodies against proinsulin antigen group are observed and a strong correlation is found between HLA-DRB1*04, DQB1*0302 and these antibodies in children with pre-type 1 diabetes. The immune activation of HLA-DRB1*04, DQB1*0302 associated with insulin reactive B or T cells is the common characteristic of the disease at the beginning.

Autoimmunization may occur at any stage of life (4). There is no typical progression process in the development clinical diabetes after the detection of islet autoantibodies. It may take weeks or years. Beta-cell function loss measurement is an indicator for the progression to the clinical disease (5). In many individuals, a progression to clinical disease does not occur even though they present immunologic markers and genetic predisposition. This situation has been associated with successful regulatory immune response. HLA DQB1*0602 allele and protein tyrosine phosphatase non-receptor type 2 (PTPN2) gene have been suggested as potential markers for predicting immune regulatory status. HLA DQB1*0602 associated with insulin reactive B or T cells is the common characteristic of the disease at the beginning. Autoimmunization may occur at any stage of life (4).

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**Pre-type 1 diabetes**

Pre-type 1 diabetes, in clinical terms, is the period of islet beta cell destruction that has the necessary amount of beta cell function and mass to maintain glucose homeostasis. Researchers and physicians agree that type 1 DM treatment should start during the quiet diabetogenic attack, which constitutes the early stages of beta cell destruction. Diagnostically ‘ongoing beta cell destruction’ is difficult to determine, it could be done by administering combination tests to high-risk patients (15). So far, important studies are held to determine the risk of type 1 DM and phased approaches were adopted (Figure 1).

**Genetic Markers**

According to current data, HLA, insulin, PTPN22, IL2Ra and CTLA4 are genetic predisposing genes. Genes predisposing to type 1 DM, except insulin gene, are associated with immune functions (16). Patients with a family history of type 1 DM have 10-15 times higher disease risk than those without a history. 70% of patients carry the HLA genes yet the disease develops only in 3 to 7% of them (17). Family history and/or genetic risk in the presence of HLA class II genotype is the first indicator. So, we should focus on relatives of diabetic subjects, especially twins, carrying the HLA DR3/4-DQ2/8 heterozygous genotype (18).

Advanced genetic analysis should be administered to autoantibody-positive individuals to exclude protective HLA class II genes.

![Figure 1. The reflection of the risk of diabetes on the progression and stages of the disease](image-url)
Anti-islet autoantibodies associated with diabetes
Autoantibodies should be measured in patients with high genetic risk. It is significant to have it administered from the age of 1. The most important predictor of developing diabetes is the number of autoantibodies, rather than their type. In BABYDIAB study, none of the children progressing to diabetes have single antibody (17,19). Among the patients with multiple numbers of diabetes-related antibodies, diabetes have developed in almost all of them in the long-term. Studies have shown that the presence of two or more antibodies will lead to very high risk and it was very rare that they are found to be transient (20,21). Autoantibodies, however, may fluctuate or completely disappear as well. ICE 512, insulin and GAD 65 may be examined often while ZnT8 has been used only in clinical studies or researches (22).

Islet-specific T Cell Assays
Despite the well-known presence of T cells in the pathogenesis of the disease, autoreactive T cells are not routinely examined. Although the recent data determined a limited contribution of the T-cell assays, especially regarding the CD4 responses, these cells were reported to reveal 75% sensitivity and 100% specificity, that is when used with autoantibody studies, in differentiating type 1 DM from healthy controls (23). Treatments given in the very early stages may either prevent the disease or exacerbate it in cases of detectable autoreactive CD8 T cells in the periphery (24,25).

Metabolic Screening
In their study Oresic and his colleagues have identified increased serum levels of lysophosphatidylcholine and hence overt autoimmunity before the emergence of islet autoantibodies (26). This method can be used in scanning of prediabetic individuals if it gets supported by large studies such as BABYDIAB, DAISY, PANDA, TEDDY.

Beta Cell Mass
According to the data obtained from the pathology specimens, only 10 to 30% of beta-cell mass remains in long-term diabetic patients. At the beginning, upon the diagnosis of diabetes, the remaining amount of beta-cell mass is unknown. The only reliable marker in non-invasive beta-cell imaging and determining its amount is monoclonal antibody IgG that uniquely connects to cell surfaces (27). Beta-cell function in autoantibody-positive patients should be evaluated through intravenous glucose or meal challenge test. Recently, the insulin requirement of the body was found to be effective in the determination of clinical diabetes (15).

Prevention Studies
Numerous immunosuppressive, immunomodulatory and different group drugs have been studied alone or in combination to prevent type 1 DM. Most of these studies involve uncontrolled and few patients. The purpose of these studies were to suppress pathogenic autoreactivity, to maintain or restore beta-cell mass and to provide good metabolic control. However, the individuals in the study group should not get affected or harmed since they have not developed diabetes yet (15). Prevention studies can be evaluated from several angles at different stages of the disease (Table 1). Stimulated C-peptide levels higher than 0.2 pmol / ml is associated with positive responses to the treatment (28). Prevention studies can be performed prior to the development of autoimmunity (primary prevention, risk cases), after the development of autoimmunity (secondary prevention) and after the development of the disease (tertiary prevention) [29].

Primary Prevention
Short-term breast milk feeding, cow's milk proteins, early exposure to grains or berries and berry-like fruits has been suggested as risk factors for beta-cell autoimmunity and clinical type 1 diabetes (30). In a study involving 230 infants fed with breast milk, carrying the HLA risk genotypes and having families with a history of type 1 diabetes, two separate groups were created randomly, one received conventional cow's milk-based formula, other group got formula containing casein hydrolyzate. After 10-year follow-up, in 33 and 17 cases, respectively, enhanced at least one autoantibody (31). In the study aiming a reduction of type 1 DM in genetically high risk patients (TRIGR), which is an international, double-blind, randomized, placebo-controlled study, 10 years of follow-up, 5606 newborns having family history of diabetes and 2159 newborns carrying HLA risk genotypes were included. This study intends to determine two more diabetes-related autoantibody positivity and the incidence of diabetes. The results are planned to be evaluated 2 times, in early 2013 and 2017 (30).

The BABYDIET study has investigated the effect of gluten intake delay on islet autoimmunity in high-risk relatives of patients with type 1 DM. It has been shown that a later exposure is safe but that does not prevent autoimmunity (32).

Omega-3 polyunsaturated fatty acids regulate the inflammatory response. A relative deficiency of Omega-3 fatty acids causes increased inflammatory reaction, and thus may result in autoimmune diseases. In a study involving children with increased genetic risk, an increase in dietary intake of omega-3 fatty acids has been observed to cause decreased islet autoantibody response (33). A study called ‘dietary prevention of Type 1 DM by docosahexaenoic acids’ studies on pregnant women in their third trimester, whose first-degree relatives have type 1 DM, and infants up to 5 months. This study is still continuing.

Based on case-control studies, vitamin D supplementation during early infancy is thought to have a protective effect on type 1 diabetes. In a study including 10,000 children, it is observed that diabetes developed less in patients who regularly took 2000 units/day of vitamin D than in those who did not (34). Phase 1 vitamin D addition study is an ongoing research including patients with increased genetic risk in the general population. Pre-pointer (primary oral/intranasal insulin trial) study researches the effectiveness of the application of mucosal human insulin on primary prevention in high-risk relatives (35). This study has not been completed yet.

Secondary Prevention
The risk of developing diabetes within 6 years has been found more than 90% in children with impaired glucose tolerance and multiple autoantibodies positivity (36). Secondary prevention covers studies using different agents in preventing the disease at this stage. Nicotinamide ensures the repair of DNA and limits the damage by supplying nicotinamide adenine dinucleotide that is a free radical scavenger or a coenzyme in damaged cells. In the European
Nicotinamide Diabetes Intervention Study (European Nicotinamide Diabetes Intervention Trial, ENDIT) including 552 individuals between 3 to 40 years-old, having first-degree relatives with type 1 diabetes and islet cell autoantibody-positive, the risk of developing diabetes in 3.3 years of follow-up was found to be similar between the patient group receiving nicotinamide (1.2 g /m²/day) and the placebo group. As such, it has been shown that nicotinamide does not delay the disease.

In non-obese mice (NOD) studies, insulin has been shown to convert insulitis from destructive response to protective response (38). Such immunomodulatory effects of insulin have been investigated in people, in newly diagnosed type 1 diabetes patients and high-risk groups. A Finnish Diabetes Prediction and Prevention study has shown that intranasal insulin does not prevent or delay the development of the disease (39). This research studied 116,720 infants without a family history yet carrying high-risk genotypes. About 15% of them were found in medium or high-risk group and 224 patients were randomized (intranasal insulin, 1U/kg/day). Most of the patients did not show any symptoms at the time of the diagnosis. 339 high-risk individuals (the risk of developing diabetes over 5 years was > 50%) were chosen for the Diabetes Prevention Trial -1 (DPT-1). They had high-titer insulin autoantibodies and low insulin response against glucose during the early phase. The placebo group was kept under close observation while the patient group was administered continuous insulin infusion for 4 days in a year and low-dose subcutaneous insulin (ultralente insulin, 2/day, 0.25 U/day) (40). After 3.7 years follow-up in average, risk of developing diabetes in both groups was similar: 42% and 41%, respectively. In the same study, 372 medium-risk patients (the risk of developing diabetes over 5 years is > 26%-50%) were placed in two groups, taking oral insulin (7.5 mg/day) and placebo. It is observed that oral insulin had no effect on delay or prevention of the disease, except a small beneficial effect observed in a subgroup with high IAA (n ≥ 80 U/ml) levels (41).

Immune therapies specifically targeting the onset of the autoimmune process may be available in the future. In a study in France involving prediabetic cases, interleukin-2 molecule conjugated with diphtheria toxin (DAB486-IL-2) was generated which targeted activated T cells. Low-dose cyclosporine was administered after seven days of infusion. DAB-IL-2 was considered to slow down the ongoing insulitis by destroying activated T cells in islets; and cyclosporin was thought to maintain the remission (42). Isoform of Glutamic acid decarboxylase, which is 65 kilodaltons (GAD-65), is a major autoantigen in patients with type 1 diabetes. It has been shown to slow down the progression of the disease when given to NOD mice in prediabetic period (43).

### Tertiary Prevention
The purpose of these studies is to maintain or increase the

<table>
<thead>
<tr>
<th>Table 1. Type 1 DM intervention studies</th>
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<tbody>
<tr>
<td><strong>Newly diagnosed DM (to maintain beta cells reserves)</strong></td>
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<tr>
<td></td>
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<tr>
<td><strong>Completed</strong></td>
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<tr>
<td>Metabolic benefits provided</td>
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<tr>
<td>Cyclosporin</td>
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<tr>
<td>Azathioprine and glucocorticoids</td>
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<tr>
<td>Anti-CD5 monoclonal antibody and ricin A chain (immunotoxins)</td>
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<td>Intensive insulin therapy Plasmapheresis anti CD3 monoclonal antibody</td>
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<tr>
<td>GAD vaccine</td>
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<tr>
<td>Anti CD20 monoclonal antibody rituximab</td>
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<tr>
<td><strong>Ongoing studies</strong></td>
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<td>Repeated doses of anti-CD3</td>
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<tr>
<td>Timoglobulin</td>
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<tr>
<td>IL2 and rapamycin (sirolimus)</td>
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<tr>
<td>Intensive metabolic control</td>
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<td><strong>Antibody positive relatives posing disease risk</strong></td>
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<tr>
<td>Studies completed without benefit</td>
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<tr>
<td>Parenteral insulin</td>
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<tr>
<td>Nicotinamide</td>
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<tr>
<td>Oral insulin (excluding subgroups) nasal insulin</td>
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<tr>
<td>Newborn or neonate (to prevent autoimmunity and diabetes)</td>
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<td>Omega 3 fatty acids</td>
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remaining beta-cell mass after the occurrence of diabetes, to reduce hypoglycemia and the development of microvascular complications and also to ensure good metabolic control to extend the honeymoon period. The clinical significance of this treatment is its effect on disease progression and the success in making endogenous insulin secretion insulin-independent. So far many antigen specific and non-specific agents are tested (29).

Immunomodulators

Azathioprine is an immunosuppressive drug that prevents or inhibits T cell responses to antigen. In a randomized, double blind study, 46 patients received azathioprine and glucocorticoid treatment. 10 individuals out of 20 in the patients group and 2 individuals out of 20 in the placebo group left the insulin treatment. Endogenous insulin secretion was improved. However, only three of the cases treated remained in remission for a year (44).

Mycoophenolate mofetil (MMF) inhibits the proliferation of T and B lymphocytes. In a multicentered randomized study, 126 Type 1 diabetes patients, who were diagnosed within 3 months, divided into 3 groups as patients who got only MMF treatment; who got MMF and Daclizumab (anti-IL-2 receptor monoclonal antibody) treatments together, and who got placebo drugs. C peptide levels viewed with mixed meal tolerance test 2 years after the treatment did not show any significant difference (45).

AntiCD3 has an effect on T cell activation and it induces energy and apoptosis in activated cells. AntiCD3 also provides immune tolerance in adaptive Treg cells in the long term (46).

Two separate Phase 2 studies using teplizumab and otelixizumab (human anti CD3) have shown that the beta cell function assessed by C peptide response was maintained, HbA1c levels were decreased, and insulin requirement was reduced in the group who were under treatment for over 2 years. In a multi-centered, 80 patient study, anti-CD3 treatment for six consecutive days was compared with placebo. Residual beta cell function on 6th, 12th and 18th months were better in the treated group, and patients didn't need an increase in insulin doses. However, side effects were observed during anti-CD3 treatment such as fever and acute mononucleosis-like syndrome following the rash treatment (47). Recent follow-up studies reveal that one dose has beneficial effects up to 5 years (48). DEFEND-1 and PROTEGE studies are ongoing phase 3 studies (29).

CD20 is involved in the activation and development regulation of B lymphocytes. Anti CD20 causes depletion of B lymphocytes selectively. The actual mechanism of rituximab in patients with type 1 diabetes is unknown. It is thought that Anti CD20 reduces the production of proinflammatory cytokines in pancreas or pancreatic lymph nodes, which increases immune response. Also, antigens presented by B lymphocytes, which are required in the activation of T lymphocytes, may be affected. In a phase II study including newly diagnosed type 1 diabetes patients, 4 doses of rituximab was given and it has been reported that this treatment partially protected beta cell function over a period of one year (49). Anti-B lymphocytes can be tested in patients with newly diagnosed diabetes, as well as human anti-CD20 antibodies.

The potential beneficial effects of anti-thymocyte globulin (ATG) in treating type 1 diabetes are not well known. ATG therapy has been shown to ensure remission in NOD mice. In a study, which is still in progress, managed by Immune Tolerance Network and Trialnet, groups were arranged as patients taking placebo and patients treated by rabbit ATG (6.5 mg/kg, 4 days). Expected results of the study are a persistent endogenous insulin secretion and a reduction in exogenous insulin requirement.

In a phase 2 study in patients diagnosed with Latent Autoimmune Diabetes of Adults (LADA), 20mcg/g GAD-alum was given to the patients and it had been shown to preserve residual insulin secretion. In a randomized study in newly diagnosed (within 18 months) type 1 diabetic adults and children, recombinant human GAD-65 vaccine form (GAD-alum) was given and compared with placebo. After 15 months, the fasting C-peptide levels or insulin requirements between two groups did not differ. Besides, GAD-specific immune response was found in GAD vaccinated children (50). Bacillus Calmette-Guerin (BCG) was found to be successful in immunomodulation in NOD mice, and then it was given to 17 patients with newly diagnosed type 1 diabetes in a pilot study. In 11 patients, remission up to 10 months was observed (51). In a larger study involving seventy-two patients, patients were separated in two groups as patients treated with BCG and nicotinamide and patients treated with BCG only. On the third month, the number of patients in remission was three in each group but on the twelfth month, remission has not been detected in any group (52).

Diapep277 is a peptide consisting of 24 amino acids and it was obtained from human heat shock protein 60. It induces anti-inflammatory T cells and by blocking B cell destruction it provides immune modulation. Diapep277 re-establishes the balance in the immune system by increasing the production of Th2 cytokines and creating a strong signal for Th2 cells. In phase 2 clinical trials with adults with Type 1 diabetes, it has been proved that beta cell destruction got stopped and c-peptide got protected significantly (53). In eighteen-month follow-up, average c-peptide levels returned to normal limits and the necessary dose of exogenous insulin to capture the same HbA1c levels of patients in standard treatment seemed reduced.

In addition, studies of CTLA4-Ig (abatacept) monotherapy phase II, anti-IL1-beta antagonist (Canakinumab) phase II and anti-IL1-alpha antagonist (Anakinra) Phase II / III are still continuing (15). When an immune therapeutic agent will be selected, the patient population and disease stage are considered. Also, the risk-benefit ratio, screening and treatment costs, length of treatment and whether it is better compared to intensive insulin therapy should be considered.

Anti-inflammatories

Tumor necrosis factor-alpha (TNF-alpha), interleukin-1 and type 1 interferons are the first cytokines proven to have direct cytotoxic effects on beta-cell function (54). Etanercept binds to TNF-alpha and inhibits the biological activity of TNF alpha. In a 24 week study with 18 patients participated, etanercept was compared to placebo, and patients who got etanercept therapy had lower HbA1c (5.9%, 7%) and higher c-peptide levels (55).

Interferons are cytokines that have multifunctional immunomodulatory effects on the cytokine cascade by their anti-inflammatory properties. In a study with 128 patients, twelve months
of oral human recombinant interferon alpha-2a (IF-A, 5000 units / day) treatment was compared to placebo. In patients who received IF-α; in stimulated mixed meal test, c peptide loss was less, but A1C or insulin requirements did not change (56).

Other Studies
The effectiveness of aggressive insulin therapy in type 1 diabetes is tested. An improvement in metabolic function is shown by applying enough insulin to suppress endogenous insulin secretion with the closed-loop system. Immunomodulatory effects of intensive insulin therapy are known. However, the results presented here may be the result of the change in the immune response of islet cells due to decrease in the metabolic requirements of the tissues (57). Hematopoietic stem cell transplantation inhibits memory T cells effect during the maturation of new lymphocyte progenitors that doesn’t participate in the anti-self activity. Allogeneic stem cell transplantation is increasingly used in the treatment of autoimmune diseases. In one study, 15 newly diagnosed patients (mean age: 19.2 years) had autologous non-myeloablative stem cell transplantation treatment (58). 13 patients did not need exogenous insulin from 1 to 35 months (mean 14.8 months). There was no control group in the study. Stimulated C-peptide peak levels were determined in 11 patients at the sixth month, and 4 out of 4 patients who got into the study on the twenty-fourth month. During the follow ups (in 29.8 months on average) 8 more patients were included in the study, 24 and 36 months later, improvement in C-peptide levels continued and insulin treatment was discontinued in 12 patients completely, and in 8 patients temporarily (59). IA-2 and insulin autoantibodies were used for the confirmation of Type 1 diabetes diagnosis, but the stem cell studies requires at least three (GAD-65, IA-2 and insulin autoantibody) autoantibody markers while including patients to the study. At the same time the number of patients in this study is small and the follow-up period is short. Possible side effects such as febrile neutropenia, nausea, vomiting and alopecia were not specified clearly. 2 patients developed pneumonia and 1 patient developed premature ovarian failure. That is why the role of stem cell transplantation for treating type 1 diabetes is not clear. While trying to stop the autoimmune attack, it should not be forgotten that a significant portion of beta-cell mass is dysfunctional at the time of clinical diagnosis, so the functional islet beta-cell mass must renew itself (60). This is only possible with beta-cell regeneration, increase in insulin production and the protection of the existing islets. Immunomodulator therapy alone does not seem to be sufficient because immune beta cell apoptosis continues after the treatment as well. Recently it is proven that beta-cell mass is a dynamic entity and can expand in order to meet a need for metabolic demands but it is not known whether similar islet mass growth is possible after the effective immunotherapy (61). Beta cell regeneration may be possible with the stimulation of insulin secretion, islet neogenesis from progenitor cells, islet transplantation and stem cell transplantation. Incretin hormone glucagon-like peptide-1 (GLP-1) analogs stimulate insulin secretion in the remaining beta cells. It has moderately delayed diabetes in NOD mice. Exenatide therapy still continues as Phase IV studies, but exenatide and daclizumab combined therapy has not been successful (62).

Apart from these, Type 1 Diabetes TrialNet group (Diabetes Research Institute, Miami, USA) is planning 4 prevention studies. Trialnet oral insulin study is a multicentered, randomized, double-blind, placebo-controlled study with a primary objective of investigating the effects of 7.5 mg / day oral insulin to the development of clinical diabetes. Patients include non-diabetic relatives of Type 1 DM patients. They had at least two positive autoantibodies, one of them being an insulin autoantibody. Patients included had normal glucose tolerance and they were aged between 3 to 45. And their 5-year relative risk of developing diabetes was approximately 35%. GAD-alum Prevention Study began by mid-2009 as multicentered, randomized, double-blind, placebo-controlled study. This study includes non-diabetic relatives of type 1 diabetic patients, who were GAD autoantibody-positive, 3 to 45 years old and their 5-year risk of developing diabetes was approximately 25%-50%. Prevention study planned with AntiCD3 monoclonal antibody includes relatives of diabetic patients with the ages of 8-45 and with a very high risk of type 1 diabetes (i. e. dysglycemia and at least two autoantibody positivity). It is a double-armed, multicentered, controlled clinical trial. Finally, Nutritional Intervention to Prevent (NIP) Type 1 Diabetes Pilot Trial study takes children who carry high-risk HLA genotypes for type 1 diabetes and gives them omega 3 fatty acid, docosahexaenoic acid (DHA) and nutritional support during the last trimester of pregnancy and the first year of their life, and then investigates its effect on the development of islet cell autoimmunity (63,64).

References


