Prevention of type 1a diabetes mellitus*


Abstract: Type 1 diabetes begins with the progressive autoimmune mediated destruction of the insulin-producing beta cells. When sufficient beta cell function is lost, the endocrine phase, characterized by insulin deficiency and hyperglycemia, supervenes. While a genetic predisposition to diabetes is an important precondition, most believe an environmental factor or factors serve as the trigger for initiating this process. In this paper we review trials designed to prevent or delay the clinical onset of diabetes. In these studies, high-risk individuals are identified by their genetic predisposition to diabetes, and/or by the presence of immune markers indicating activation of the autoimmune process directed against islet cells. The Deutsche Nicotinamide Intervention Study (DENIS) randomized 55 high-risk subjects to either nicotinamide or placebo and found no significant benefit. The European Nicotinamide Diabetes Intervention Trial (ENDIT) completed enrollment in May 1998. ENDIT screened over 40000 relatives, randomizing 552 to either nicotinamide or placebo. Results are expected in May of 2003. Designed to test if avoidance of cow’s milk in infancy will decrease the incidence of diabetes, the Trial to Reduce Type 1 Diabetes in the Genetically at Risk (TRIGR). High-risk infants are randomly assigned to different supplemental formulas in the first 6 months of life. Initial results suggest that removing cow’s milk has a protective effect. The ongoing, NIH funded, multicenter Diabetes Prevention Trial – Type 1 (DPT-1) is testing two antigen-based (insulin) interventions in relatives at high risk for diabetes. Now in its sixth year, the DPT-1 study group has screened over 84000 individuals. As of November 2000, 339 subjects have been randomized in the parenteral insulin study, completing the enrollment phase. Enrollment continues in the oral insulin study. Results of this trial are not yet available. Different epitopes of insulin and its analogs, monoclonal antibodies, and cytokine-based therapy, among others, have all been proposed as potential new interventional agents. While a great deal of effort will be required to test these approaches, the potential benefits of prevention justify these research efforts.

Type 1a diabetes mellitus [T1aDM (1)] is a serious, expensive, life-limiting disease, worthy of both prevention and cure. T1aDM results in insulin deficiency secondary to autoimmune mediated destruction of β cells (2). The interaction between a susceptible immune phenotype, coupled with other genetic factors, and some elements from the environment (3) likely invokes this inappropriate assault on the β cells by activated T cells. Each different immune phenotype may have its own set of triggers, greatly complicating their identification (4).

The autoimmune pathogenesis of T1aDM directs the efforts to prevent it. Susceptible individuals are identified by searching for evidence of autoimmune activity directed against β cells. While direct evaluation of T-cell activity might be preferable, antibody determinations are generally used for screening because these assays are more robust. Antibody titers are often used in combination with an assessment of the genetic susceptibility, primarily evaluated by human leukocyte antigen (HLA) typing.

Interventions are generally designed to delay or

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prevent T1aDM by impacting some phase of the immune pathogenesis of this disease. As discussed below, current trials are attempting to modify the course of disease progress at many points along the presumed pathogenic pathway. Most prevention trials include only relatives of known diabetics, a group in which risk prediction strategies are most established. Trials in genetically at-risk patients are studying whether avoiding one of the putative environment triggers for T1aDM can delay or prevent its onset. Studies with nicotinamide are testing if interfering with aspects of cellular destruction can alter the course of prediabetes. Trials with insulin are testing the hypothesis that antigen-based therapies can delay or prevent progression to T1aDM.

In this paper, we review the current status of five large, randomized, controlled, intervention trials and summarize the future for prevention of T1aDM.

Nicotinamide

The active agent in the first two studies is nicotinamide (also know as niacinamide, vitamin B3). Nicotinamide has multiple actions (5,6), which could modify the processes thought to contribute to the progressive β cell destruction associated with T1aDM. First, nicotinamide inhibits poly [adenosine diphosphate (ADP)-ribose] synthetase (OMIM#173870), an enzyme that is required for cellular repair. Single-strand breaks in DNA induce this enzyme and its activation consumes nicotinamide adenine dinucleotide (NAD). Over-activation depletes cellular stores of NAD(+) and decreases adenosine triphosphate (ATP) levels, resulting in cell death. Of interest, disruption of the gene encoding this enzyme in mice reduces their sensitivity to streptozotocin-induced diabetes (7–9). Nicotinamide therapy restores cellular NAD(+) levels and helps to prevent damage from cytokines [interleukin 1 (IL-1)] (10). Other reported actions of nicotinamide include protection against oxygen free radicals (11,12), and decreased MHC class II expression (13).

Nicotinamide has shown promise in a number of studies using animal models of T1aDM (14). Because of these animal studies, and since nicotinamide is well tolerated without significant side-effects, many have advocated its use in humans. Pozzilli and Andreani (15) have reviewed the use of nicotinamide in 10 randomized (five placebo-controlled) trials involving 211 patients with recent-onset T1aDM. While there were no differences in insulin dose or glycosylated hemoglobin concentration, fasting C-peptide levels were higher in the nicotinamide treated patients [0.73 ± 0.65 (weighted SD) vs. 0.32 ± 0.56 ng/mL, p < 0.05] one year after the clinical diagnosis of diabetes.

There have been a number of small studies of nicotinamide in subjects at high risk of developing diabetes (16–18). In the largest study, Elliot et al. (19) conducted an approximately randomized design incorporating all students 5–7.9 yr of age in Auckland, New Zealand, testing both nicotinamide as an intervention and the feasibility of prevention trials in the general population. While its complex design makes interpretation challenging, the data suggest that nicotinamide reduces the rate of T1aDM. Taken together, these data form the basis for the two large randomized nicotinamide trials discussed below.

Deutsche Nicotinamide Intervention Study (DENIS)

DENIS (20) was a randomized, placebo-controlled trial testing the hypothesis that nicotinamide could have a dramatic effect on the risk subjects developing diabetes. Two-thousand-four-hundred-and-fifteen siblings of type 1 diabetics from Germany and Austria, aged 3–12 yr, were screened using an islet cell antibody (ICA) assay. Those siblings with confirmed ICA titers of greater than or equal to 20 JDF (Juvenile Diabetes Foundation, units and a non-diabetic oral glucose tolerance test (OGTT) were eligible. One-hundred-and-sixty-four siblings had sufficiently high ICA titers and 68 families agreed to be randomized. Thirteen families revised their decision following randomization and 55 subjects entered the trial. The investigators assumed a progression rate of 30% over 3 yr and designed this trial to have sufficient power to detect a reduction to 6% (power of 90%, alpha of 0.05), a target for a drug effect that the authors themselves acknowledge as ambitious. The intervention consisted of oral nicotinamide [slow release (SR)] 1.2 g/m², divided into two daily doses, or a placebo. While the initial study protocol planned for a maximum of 5 yr of follow-up, the study was concluded after the second interim analysis demonstrated that the trial failed to detect an effect of intervention. The incidence of diabetes is essentially equivalent in both groups (Fig.1). Endogenous insulin secretion was measured using intravenous glucose tolerance tests (IVGTT). Unexpectedly, given earlier studies of nicotinamide, the first-phase insulin release (FPIR) at 2 yr was decreased in the nicotinamide group while it remained stable in the placebo group (Fig.2). No other adverse effects of treatment were noted.

The European Nicotinamide Diabetes Intervention Trial (ENDIT)

ENDIT (21) is a large multinational study designed to test the efficacy of nicotinamide in high-risk subjects. Approximately 50 000 subjects, first-degree relatives of children with type 1, between the ages of 5
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and 40yr across 20 countries were screened. Enrollment started in June of 1994 and was completed in the first half of 1998 when 552 subjects with positive ICA titers (greater than or equal to 20 JDF units with a confirming sample of greater than or equal to 5 JDF units) and a non-diabetic OGTT were enrolled into this randomized, masked, placebo-controlled trial. Follow-up of subjects in this trial continues.

In designing ENDIT (Table 1), the investigators assumed that 40% of subjects would progress to diabetes over 5yr and designed this trial to have sufficient power to detect a 35% reduction (211 subjects in each group, power of 90%, alpha of 0.05).

Intervention consisted of oral nicotinamide (SR), 1.2g/m² divided bid, or placebo. Results of this large study are expected in May 2003. Of note, an interim analysis done in September 1998 demonstrated that none of the a priori criteria for stopping the study had been met. Specifically, the data indicated that there was not a higher incidence of diabetes in the nicotinamide group using a p-value <0.0001, and that there were no significant safety concerns.

Given that DENIS did not suggest a reduction in the risk for diabetes (and in fact, showed a decrease in C-peptide at 2yr), we do not recommend the use of nicotinamide pending the completion of ENDIT.

Trial to reduce type I diabetes in the genetically at risk (TRIGR)

Identification of the environment triggers, which may interact with susceptible immune systems to cause T1aDM, is an ongoing quest. An extensive, although controversial, literature (3) suggests that cows’ milk based formulas, used for infant feeding, are one such trigger. Two cows’ milk proteins, bovine serum albumin and casein, have been implicated as the specific offending antigen. TRIGR is a series of pilot trials based in Finland designed to test the hypothesis that avoidance of nutritional cows’ milk proteins for at least the first 6 months of life will reduce diabetes in a high-risk population.

Finnish infants who have first-degree relatives with T1aDM are first genotyped to categorize their level of risk (22). Infants who have a high susceptibility for diabetes (i.e., those that are positive for DQB10302 and/or DQB1 02 and who are negative for DQB10602, 0603 or 030) are offered enrollment into the trial. Two-hundred-and-thirty-four infants have been randomized, 114 into the intervention group and 110 into the control group.

After full breast-feeding, the intervention group received a casein hydrolysate formula, while the control group received a cows’ milk containing formula. Families were advised to avoid beef and cows’ milk products in the diet. Fifteen per cent of the infants dropped out of the study before 8 months. Of note, those infants randomized into the intervention group remained breast-fed longer than those in the control group (8.1 vs. 7.2 months). Likewise, the initiation of supplementary milk feeding occurred later in the intervention group (3.3 vs. 2.2 months). Preliminary results suggest that this dietary intervention decreases the rate of anti-islet cell antibody development in high-risk infants (23). Antibodies to islet antigen 2 (IA-2), insulin, and glutamic acid decarboxylase (GAD) as well as ICA titers were measured in 173 children at the 2-yr observation point. Three of 84 children (3.6%) in the casein hydrolysate intervention have developed at least one autoantibody compared with 10 of 89 (11.2%) in the control group (p = 0.056, Fisher’s exact test).

While these are only preliminary results, breast-feeding has substantial additional benefits and few, if any, significant risks and we believe that it should be generally advocated.
Diabetes prevention trial – type 1 (DPT-1)

At the time the DPT-1 was initiated, it had been well established that T1aDM is an autoimmune disease, yet the risks of using potent immunosuppressive agents at the clinical onset of T1aDM did not appear to outweigh potential benefits. Immunotherapy with cyclosporine A had been shown to be effective in transient preservation of endogenous insulin secretion after onset of clinical diabetes (24), but the effect was not permanent (25), and some subjects developed interstitial nephritis (26). Family studies had indicated that anti-islet cell antibodies were present for years before clinical onset of diabetes (27). When the titers of ICAs and insulin autoantibodies were combined with an assessment of endogenous insulin production (FPIR), it was possible to estimate the risk for developing T1aDM (28).

Animal studies had demonstrated that oral or parenteral insulin administration could delay or prevent onset of diabetes. In two animal models of spontaneous autoimmune diabetes, daily insulin injections to prediabetic biobreeding (BB) rats (29–32) or non-obese diabetic (NOD) mice (33,34) inhibited the development of diabetes and decreased insulitis. Two potential mechanisms have been suggested. First, exogenous insulin administration promotes β cell rest, diminishing production of β-cell enzymes and proteins that may act as autoantigens. Secondly, exogenous insulin could induce immune tolerance to this autoantigen.

Human studies documented that intensive insulin therapy at the onset of diabetes (3.5 U/kg/d of i.v. insulin by an ‘artificial pancreas’) resulted in sustained islet cell function for 1 yr following initial treatment (35). This could be secondary to decreased islet cell destruction due to prevention of ‘glucotoxicity’, or it may be secondary to an alteration in the immune system achieved by β-cell rest and decreased expression of islet autoantigens. Several pilot studies have shown that infusions of i.v. insulin over 5–7 d, coupled with daily subcutaneous insulin, can delay onset of diabetes in individuals at high risk for T1aDM. Keller et al. (36), in a non-randomized trial, treated five subjects with i.v. insulin infusions (average dose 0.54 U/kg-d) every 9 months coupled with daily subcutaneous insulin (average dose 0.22 U/kg-d). The treated group was compared to a cohort of seven patients who refused treatment. The groups were not matched for initial first-phase insulin response, with the control lower (32 uIU/mL) than the treated group (50 uIU/mL). After 5 yr, 60% of subjects in the actively treated group remained non-diabetic while the entire control group had progressed to diabetes within 3 yr. This pilot study was initially used in developing the design of the DPT. Fuchtenbusch et al. (37) randomized 14 prediabetics (seven to control and seven to treatment). The two groups were initially equally matched for FPIR, ICA titers, and number of autoantibodies (IAA, GAD, IA-2). The treatment group received i.v. insulin infusions (initial dose 0.1 U/h) for 7 d followed by daily SC injections for 6 months (0.17–0.68 U/kg-d in 2–4 injections/d). The 7-d insulin infusion was repeated annually, but no additional SC insulin was given after 6 months. At 4 yr of follow-up, 6/7 in the control group developed diabetes, and only 3/7 treated with insulin had developed diabetes (p = 0.028).

The oral arm of the DPT-1 was based on several experimental animal models of autoimmune diseases where oral antigen therapy with disease specific antigens had demonstrated protection from disease progression (collagen in rheumatoid arthritis, myelin basic protein in multiple sclerosis, and insulin and GAD in diabetes) (38). Oral administration of insulin prevents onset of diabetes in the NOD mice through a T-cell-dependent activation of a TH2 response (39). This protection can be transferred using CD4+ T-cells from oral-insulin-treated animals to animals who have already developed insulitis, demonstrating that oral-insulin treatment induces ‘bystander suppression’ of insulitis (40,41). The dose of oral antigen is important because low doses may stimulate the im-
mune response, whereas higher doses may induce anergy or deletion of antigen specific T cells (42).

The DPT-1 screens first- and second-degree relatives of a person with T1aDM (defined as onset of diabetes before age 40 yr and on insulin therapy within 1 yr of diagnosis). Potential subjects are screened for the presence of ICA titers greater than or equal to 10 JDJ units. Risk for diabetes is further defined by doing an i.v. glucose tolerance test to determine FPIR, and the presence of a protective HLA allele (DQB1*0602) is determined. If the protective allele is absent and the FPIR is less than the 10th percentile for age on two separate occasions then subjects are considered at high risk for diabetes (greater than 50% within 5 yr). If these subjects do not already have diabetes, as determined by an OGTT, they are eligible for the parenteral arm of the study. In the parenteral, or high-risk, arm, subjects are randomly assigned to receive either no treatment or parenteral insulin. The parenteral insulin is a combination of i.v. insulin for 4 d once a year to suppress endogenous insulin production. The initial infusion rate of 0.015 U/kg.h is adjusted, based on frequent glucose determinations. Subjects also receive 0.25 U/kg.d of ultralente insulin divided into two equal doses.

Subjects with a normal FPIR who have two autoantibodies (ICA and IAA) are considered at moderate risk of developing diabetes (25–50% over 5 yr). These subjects are eligible for the oral trial, if they have a normal oral glucose tolerance test. Subjects are randomly assigned to receive either oral insulin (7.5 mg po once daily 1/2 h before breakfast) or a placebo in a blinded fashion. Subjects in both the parenteral and oral arms of the study are monitored for the development of diabetes at frequent intervals.

The initial sample size projected for the parenteral antigen protocol is 340 subjects (Table 1). This sample size provides a power of 80% to detect a 35% difference in the annual hazard rate for the onset of diabetes, expected to be 21% per year in the control group (allowing for a 10% drop-out rate). The sample size projection for the oral insulin protocol is 490 subjects, with approximately equal numbers assigned to the experimental therapy and placebo control. This sample size provides a power of 80% to detect a 50% difference in the annual hazard rate for the onset of diabetes, expected to be 6%/yr in the control group, and assuming a 10% drop-out rate. As of November 2000, 84821 eligible subjects have been screened for the presence of islet cell antibodies. Two-hundred-and-ninety-three subjects have been randomized into the oral study and enrollment continues. Of note, 339 subjects have been randomized into the parenteral study and while the study continues, enrollment is now complete.

The DPT-1 is providing one of the largest natural history studies of type 1a diabetes, with studies of genetic and immunologic risk factors and of islet cell function. Because half of the study subjects are not receiving active treatment, the data obtained from these subjects will significantly improve diabetes prediction. One of the interesting subgroups defined by the DPT are those with the ‘protective’ allele, HLA DQA1*0102, DQB1*0602 (referred to as DQB1*0602) which is thought to confer protection from the onset of diabetes. Understanding the protective function of this allele may lead to future therapies in preventing type 1a diabetes. In a recent report from Greenbaum and the DPT-1 study group (43), 7.3% of 1376 ICA positive subjects had this allele, and there was a higher incidence of HLA DQA1*0102, DQB1*0602 in blacks (a 4.4 higher odds ratio when compared with Caucasians). When compared with ICA positive DQB1*0602 negative subjects, DQB1*0602 positive individuals had lower titers of ICA (40 vs. 80 JDJ units), a lower incidence of IAA (20 vs. 47%), fewer had additional autoantibodies (7% vs. 23%), and fewer had a low FPIR (13% vs. 28%). Two per cent have gone on to develop diabetes with a mean follow-up of 2 yr, demonstrating that protection form the allele is relative and not absolute.

One of the goals of the DPT was to define a group at high risk of developing diabetes, and the DPT has been successful in meeting this goal. After a subject is found to be ICA positive, it may take several months to complete the testing necessary for staging and to confirm a normal OGTT. In this interval 11% of ICA positive relatives have developed diabetes (44). Forty-two per cent developed clinical symptoms of diabetes, and 58% had hyperglycemia during staging. Almost one half of the hyperglycemic group had a normal fasting glucose, but an elevated 2-h glucose (>200 mg/dL) on their OGTT, but had no clinical symptoms of diabetes. This state of ‘silent’ diabetes may last for up to 2 yr prior to onset of clinical diabetes (45), and is not associated with insulin resistance (46). The effect of early intervention with insulin therapy in this asymptomatic group remains to be determined.

The DPT has also confirmed the predictive value of a low FPIR. Data on 1622 subjects who had FPIR assessed after having a positive ICA have recently been published (47). Lower FPIR values were reported in subjects with an impaired or diabetic OGTT, in subjects who had multiple antibodies, and in subjects with higher titers of IAA and ICA autoantibodies, confirming that a low FPIR correlates strongly with risk factors for developing diabetes.

Ancillary studies are ongoing to determine possible mechanisms of action of insulin therapy, including the effects of parenteral and oral insulin on immune regulation. The 4-d insulin infusion has been demonstrated to cause transient suppression of endogenous insulin secretion, and insulin secretion returns to nor-

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Mal levels within 3d of stopping the insulin infusion (48). The effect of antecedent infections and life stressors of the development of diabetes is also being studied, with preliminary data indicating that infectious disease before age 2yr may be a predictor of islet cell positivity, whereas stressful life events do not appear to be associated with ICA positivity (49).

Recently, two human studies have examined the use of oral insulin to improve residual islet cell function after clinical onset of diabetes. These studies used doses of oral insulin similar to the doses used in the DPT-1 (7.5 mg/d). In France (50), 131 antibody positive diabetic subjects aged 7–40yr without initial ketoadidosis were randomly assigned to placebo, 2.5 mg/d, or 7.5 mg/d of oral insulin within 2 wk of diagnosis. There was no difference between the groups in their residual insulin secretion (fasting and stimulated C-peptide levels), hemoglobin A1c levels, and insulin requirements during the 12-month study. In an Italian study (51), 82 subjects aged 5–35 yr were randomly assigned to receive placebo, 2.5 mg/d, or 7.5 mg/d of oral insulin within 2 wk of diagnosis. Again there was no difference over 1 yr in their residual insulin secretion (fasting C-peptide levels), hemoglobin A1c levels, and insulin requirements. In both studies there was no change in antibody titers to insulin. These studies are distinctly different from the DPT-1 because oral insulin was given to subjects after the clinical onset of diabetes when there are only a limited number of residual islet cells, and subjects were also receiving parenteral insulin therapy, which may also alter immune response and mask any benefit from oral insulin.

The DPT-1 Study Group continues to screen relatives to find high-risk subjects for the oral study [1-800-HALT-DM1 (1-800-425-8361)].

**Future directions in the prevention of T1aDM**

The prevention trials discussed above will add to our knowledge and improve our understanding of the pathogenesis of human diabetes. In addition, the understanding of molecular mechanisms of autoimmune diseases and diabetes, in particular, is expanding rapidly. As immune mechanisms are better delineated, new potential approaches to preventing end organ destruction are being considered. A partial list of agents under consideration (Table 2) demonstrates the broad range of possible interventions. Clearly, the difficult task of balancing the potential risks and benefits of each possible agent is complicated by the facts that potential subjects are generally healthy and are often quite young.

Both the ENDIT and DPT-1 trials demonstrate the large number of subjects at high risk of T1aDM required to directly test the efficacy of any intervention with sufficient statistical power. Intensive and expensive efforts are required to identify and recruit these high-risk subjects. Additional approaches will likely be needed to select the best agents from among the ever-expanding possibilities. Future studies may not rely on the classical immunofluorescent ICA assay, but will likely use antibodies to biochemical markers such as GAD-65, ICA-512, and IAA. These assay technologies could be done using samples obtained by fingerstick, avoiding a venipuncture.

While most screening for the risk of developing diabetes involves the measurement of antibodies, the actual destruction of β cells is mediated by T cells. A direct measure of T-cell autoreactivity could be a very rapid signal of potential efficacy. Assays of T-cell autoreactivity, however, have proven to be problematic to date (52). Other surrogate measures await improved technology.

One approach is to test possible agents in patients at onset of clinical T1aDM. As these subjects already have T1aDM, some surrogate measure of immune intervention efficacy is essential. The best current marker for maintenance or recovery of β cell function is C-peptide levels, a measure of endogenous insulin production. In addition to being a likely indication of efficacy, improved β cell function has practical clinical benefits by reducing the risk for hypoglycemia while decreasing the risk of retinopathy (53,54). Some investigators have argued that improved β cell function, even in the absence of insulin independence, is a reasonable treatment goal (55).

Likewise, a non-invasive assessment of β-cell mass

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**Table 2. Potential interventions**

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<td>Insulin</td>
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<td>Insulin-cholera toxin B subunit (Novo Nordisk)</td>
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<td>Insulin B9-B23 (Neurocrine)</td>
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<td>Insulin B chain</td>
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<td>B25-Asp Insulin (Novo Nordisk)</td>
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<td>Heat-shock protein</td>
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<td>Hsp60 peptide (DiaPep277, Peptor) – in Phase II</td>
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| **mGAD65 (Diaymd Therapeutics)** |
| **Non-mitogenic α-CD3** |
| **Interleukin-2-receptor antibody (Zenapax, Roche, daclizumab)** |
| **α-CD25 (Protein Design Lab)** |
| **α-CD154 (40) (Antova, Biogen)** |
| **α-CD40/GP39** |

| **Others** |
| **Cytokine-based** |
| IL4SA selective agonist (Bayer) |
| Lisfylline (Cell Therapeutics) |
| Conventional immunosuppression |
| Mycophenolate mofetil (Cellcept, Roche) |
| COX-2 inhibitors |
| Vitamin D analogs |
| Theramex |

Adapted from (21).
could be very informative (56). As the autoimmune attack on the β cells progresses, insulin secretory capacity appears to decrease more rapidly than the actual mass of insulin secreting cells. The clinical 'honeymoon' period in which insulin requirements fall after clinical diagnosis reflected recovery of secretory capacity. Pathological studies in new onset diabetics reveal insulin-containing cells within the islets (57,58). Maintenance or recovery of β-cell mass, if it could be measured non-invasively, would be a useful surrogate measure.

Summary

The great importance of diabetes prevention and the large number of potential interventions available for testing essentially mandate a continued cooperative approach in future studies. New agents will likely be tested in new onset patients with T1aDM, requiring both existing and novel surrogate outcome measures to assure the best selection of potential agents for the next set of large prevention trials. At this time, aside from the general merits of recommending breastfeeding, no current intervention to prevent progression to clinical T1aDM (aside from breast-feeding) has been demonstrated to work well enough to be recommended outside of well-organized clinical trials.

References

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