Effects of Oral Insulin in Relatives of Patients With Type 1 Diabetes

The Diabetes Prevention Trial–Type 1

THE DIABETES PREVENTION TRIAL–TYPE 1 STUDY GROUP

OBJECTIVE — This randomized, double-masked, placebo-controlled clinical trial tested whether oral insulin administration could delay or prevent type 1 diabetes in nondiabetic relatives at risk for diabetes.

RESEARCH DESIGN AND METHODS — We screened 103,391 first- and second-degree relatives of patients with type 1 diabetes and analyzed 97,273 samples for islet cell antibodies. A total of 3,483 were antibody positive; 2,523 underwent genetic, immunological, and metabolic staging to quantify risk of developing diabetes; 388 had a 5-year risk projection of 26–50%; and 372 (median age 10.25 years) were randomly assigned to oral insulin (7.5 mg/day) or placebo. Oral glucose tolerance tests were performed every 6 months. The median follow-up was 4.3 years, and the primary end point was diagnosis of diabetes.

RESULTS — Diabetes was diagnosed in 44 oral insulin and 53 placebo subjects. Annualized rate of diabetes was similar in both groups: 6.4% with oral insulin and 8.2% with placebo (hazard ratio 0.764, $P = 0.189$). In a hypothesis-generating analysis of a subgroup with insulin autoantibody (IAA) levels confirmed (on two occasions) ≥80 nU/ml ($n = 263$), there was the suggestion of benefit: annualized diabetes rate 6.2% with oral insulin and 10.4% with placebo (0.566, $P = 0.015$).

CONCLUSIONS — It is possible to identify individuals at high risk for type 1 diabetes and to enroll them in a large, multisite, randomized, controlled clinical trial. However, oral insulin did not delay or prevent type 1 diabetes. Further studies are needed to explore the potential role of oral insulin in delaying diabetes in relatives similar to those in the subgroup with higher IAA levels.

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The Diabetes Prevention Trial–Type 1 (DPT-1) was a randomized controlled clinical initiative designed to determine whether it is possible to prevent or delay the onset of overt diabetes in relatives of patients with type 1 diabetes. DPT-1 included two separate trials. Relatives were screened for islet cell antibodies (ICAs), and those who were positive underwent further testing to assess projected 5-year risk of diabetes. Earlier we reported the results of the DPT-1 parenteral insulin trial, conducted in relatives with >50% projected 5-year risk of diabetes (1). This article reports the results of the DPT-1 oral insulin trial in relatives with a projected 5-year risk of diabetes of 26–50%. In both trials, relatives were studied because of their 10- to 20-fold increased risk compared with the general population (2,3).

Type 1 diabetes is a consequence of immune-mediated destruction of insulin-secreting pancreatic islet β-cells (4). A number of studies have suggested that oral administration of autoantigens induces protective immunity that has the potential to downregulate ongoing destructive immune reactions (5–7). Peptides derived from an orally administered antigen encounter the mucosal gut–associated lymphoid tissue, which serves both to protect the host from ingested pathogens and to prevent the host from reacting to ingested proteins. The concept is that low doses of orally administered autoantigens suppress autoimmunity by inducing antigen-specific regulatory T-cells in the gut, which act by releasing inhibitory cytokines at the target organ (5–7). In the mid-1990s, the concept of oral antigen administration was quite popular, and studies were initiated in a number of human autoimmune diseases. In the nonobese diabetic mouse model of type 1 diabetes, oral administration of insulin to young, pre-diabetic mice inhibits their development of type 1 diabetes (8–13). Oral insulin also prevented diabetes and even reversed hyperglycemia in a transgenic mouse model of virus-induced diabetes (14). The results in these animal models suggested that oral insulin could attenuate pancreatic islet autoimmunity, leading to a delay in the onset of the disease, and was the impetus to conduct the DPT-1 oral insulin trial. Moreover, the breakdown of insulin into smaller peptides in the gastrointestinal tract would avoid any hypoglycemic effects of insulin,

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org.

Abbreviations: DPT-1, Diabetes Prevention Trial–Type 1; FPG, fasting plasma glucose; FPIR, first-phase insulin response; IAA, insulin autoantibody; ICA, islet cell antibody; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGT, oral glucose tolerance.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

an additional potential benefit for testing oral insulin.

RESEARCH DESIGN AND METHODS

— The study was divided into three parts: screening, staging, and intervention (1). Participants were recruited from study clinics and through media campaigns.

Screening

First-degree (ages 3–45 years) and second-degree (ages 3–20 years) relatives of patients with type 1 diabetes were screened for ICAs. Those with ICA titer ≥10 Juvenile Diabetes Foundation units were invited to have staging evaluations.

Staging

Staging confirmed ICA positivity, measured insulin autoantibody (IAA) status, assessed first-phase insulin response (FPIR) to intravenous glucose, assessed oral glucose tolerance (OGT), and determined presence or absence of HLA-DQA1*0102/DQB1*0602 (a protective haplotype that excluded subjects from participation) (15,16). Relatives who were ICA^+ and IAA^+ and with FPIR above threshold (defined below) and normal glucose tolerance were projected to have a 5-year risk of 26–50% ("intermediate risk") and were eligible for the oral insulin trial. Those identified as having a 5-year risk of ≥50% ("high risk") were eligible for the parenteral insulin trial previously reported (1). The original protocol had an entry criterion of confirmed (on two occasions) IAA level >5 SD above the mean of the normal reference range (i.e., ≥80 nU/ml). In October 1997, after review of data from natural history studies suggesting that a sufficient cutoff was >3 SD above the mean of the reference range, to enhance enrollment the entry criterion was changed to that level (i.e., IAA ≥39 nU/ml).

Intervention

The study was a double-masked, placebo-controlled, randomized clinical trial, in which participants were assigned to receive capsules of either oral insulin, 7.5 mg of recombinant human insulin crystals (Eli Lilly, Indianapolis, IN), or matched placebo. Capsules were prepared with methylcellulose filler at a compounding pharmacy (Belmar Pharmacy, Lakewood, CO). Masked bottles of oral insulin or placebo were shipped to clinical sites from a research pharmacy (Moffitt Cancer Center, Tampa, FL). Subjects consumed the capsule as a single daily dose before breakfast each day, either by taking the capsule or, if the subject could not swallow capsules, sprinkling its contents in juice or on food. Randomization used a central automated system, stratified by clinical center, using random variable block sizes.

Study sites

Study coordination, laboratory tests, and data management were done centrally. Protocols were approved by institutional review boards at all participating locations across the U.S. and Canada, including 91 sites conducting the intervention. Participants (and/or their parents) provided separate written consent for each part, screening, staging, and intervention, and yearly thereafter for continuation in the study.

Role of the funding source

Representatives from the sponsoring institutes of the National Institutes of Health (National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, and National Institute of Child Health and Human Development) served on the Steering Committee and virtually all of the study group committees and were full participants on their committees, which were involved in all aspects of protocol design, data analysis, and preparation of the manuscript. The other funding sources provided only resources and were not involved in the study per se.

Follow-up assessments

Participants were seen every 6 months, and at those visits an OGT test was performed to assess glycemic status, the primary study end point. An intravenous glucose tolerance test was performed at baseline, annually thereafter, and at study end. Mixed-meal tolerance tests were performed at baseline, after 3 years, and at study end.

Participants checked blood glucose if they experienced symptoms of hypoglycemia. Presumed hypoglycemia (without measurement of glucose) was defined as typical symptoms that promptly resolved with food intake. Definite hypoglycemia was defined as blood glucose <2.8 mmol/l (50 mg/dl) measured at the time of symptoms. Severe hypoglycemia was defined as loss of consciousness, convulsion, stupor, or hypoglycemia requiring assistance of another person or treatment with intravenous glucose or subcutaneous glucagon. Chemical hypoglycemia was defined by five-point (before breakfast, before lunch, before supper, 2 h after supper, 3:00 A.M.) home capillary blood glucose profiles obtained quarterly, if two of these glucose values were <2.8 mmol/l (<50 mg/dl).

Tolerance test procedures

Tolerance tests were performed after an overnight fast. Samples were drawn through a temporary indwelling intravenous catheter. Intravenous glucose tolerance tests were performed as described (17,18). Insulin values at 1 and 3 min were added to determine FPIR. FPIR was above threshold if ≥10th percentile for siblings, offspring, and second-degree relatives (≥100 μU/ml if age ≥8 years; ≥60 μU/ml if age <8 years) and ≥1st percentile for parents (≥60 μU/ml). FPIR above threshold was required for eligibility.

For the oral glucose tolerance test, the oral glucose (Sundex, Fisher) dose was 1.75 g/kg (maximum 75 g). Plasma glucose values were interpreted according to American Diabetes Association guidelines (19): fasting plasma glucose (FPG) ≥7.0 mmol/l (≥126 mg/dl) or 120-min glucose ≥11.1 mmol/l (≥200 mg/dl) was considered diagnostic of diabetes; FPG 6.1–6.9 mmol/l (110–125 mg/dl) signified impaired fasting glucose (IFG); 120-min glucose 7.8–11.1 mmol/l (140–199 mg/dl) signified impaired glucose tolerance (IGT). If a 30-, 60-, or 90-min level was ≥11.1 mmol/l (≥200 mg/dl) but FPG and 120-min levels were below threshold for IFG and IGT, this was noted as indeterminate glucose tolerance. A normal OGT during staging was required for eligibility. Diagnosis of diabetes required confirmation on a subsequent day by OGT, elevated fasting plasma glucose, or random plasma glucose ≥11.1 mmol/l (≥200 mg/dl) accompanied by symptoms of polyuria, polydipsia, and/or weight loss (19).

For the mixed-meal tolerance test, a liquid formula meal was consumed (Sustacal/Boost, Mead Johnson Nutritionals; 6 kcal/kg body weight, maximum 360 kcal).

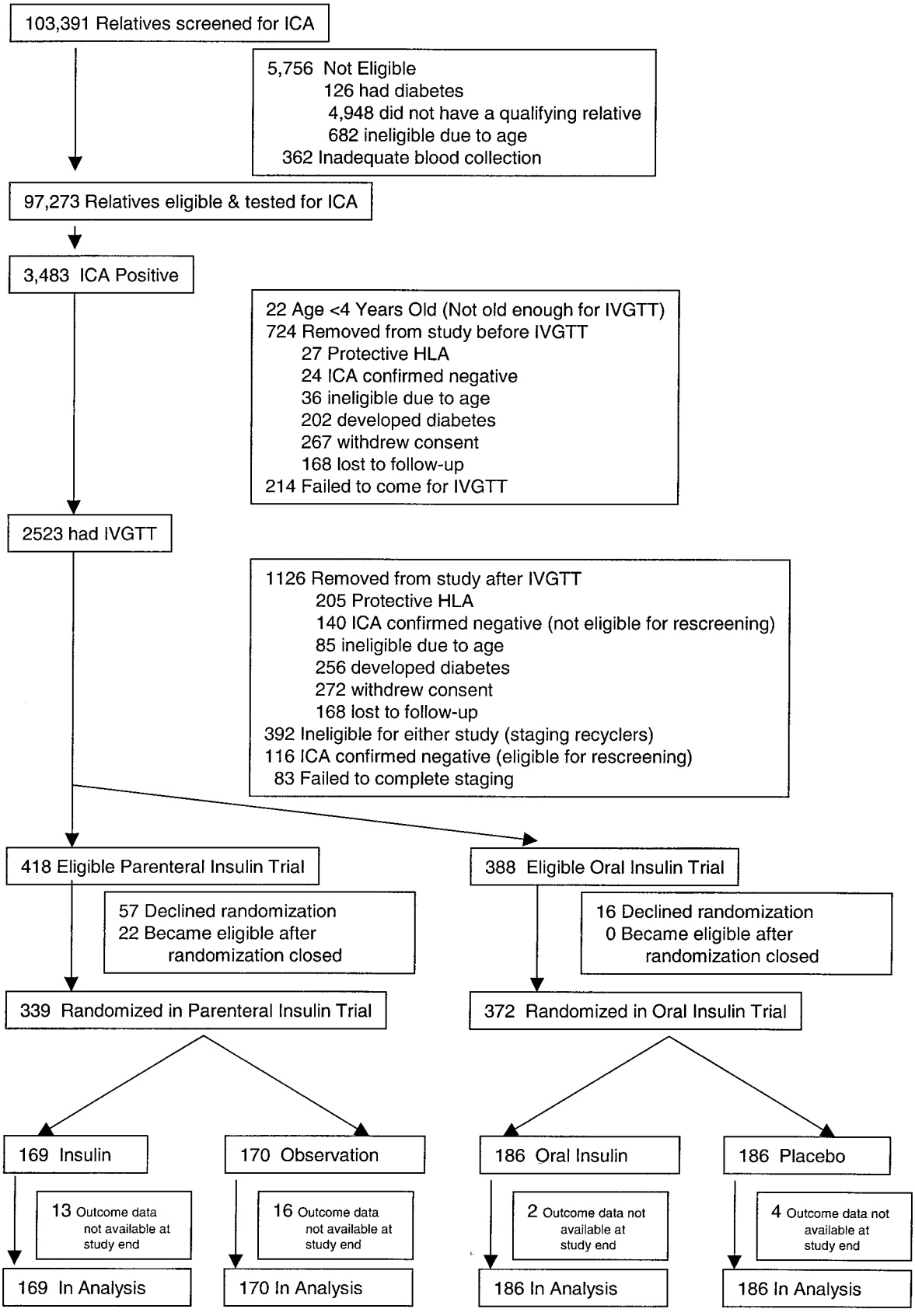

Figure 1—*Flow diagram of all subjects recruited to trial. IVGTT, intravenous glucose tolerance test.*

Table 1—*Baseline characteristics of randomly assigned subjects*

	Oral insulin group	Placebo group	*P* value
n	186	186	
Median age	11.0 (7–14)	9.5 (7–14)	0.3569
Average FPIR (μU/ml)	161.6 ± 72.4	158.9 ± 99.2	0.7672
Race			0.2807
White	164 (88.1)	163 (87.6)	
African American	5 (2.6)	2 (1.0)	
Hispanic	8 (4.3)	14 (7.5)	
Other	9 (4.7)	7 (3.7)	
Sex			0.1381
Male	119 (63.9)	105 (56.4)	
Female	67 (36.0)	81 (43.5)	
Relationship to index patient with diabetes			0.6552
Sibling	112 (60.2)	108 (58.0)	
Offspring	49 (26.3)	53 (28.4)	
Parent	11 (5.9)	7 (3.7)	
Second degree	14 (7.5)	18 (9.6)	
Antibody levels			
Median ICAs (JDF units)	80 (403–20)	80 (40–160)	0.9253
Mean IAAs (nU/ml)	382 ± 555	346 ± 436	0.4910
GAD antibodies			0.2908
Positive	144 (77.8)	136 (56.4)	
Negative	41 (22.1)	50 (43.5)	
ICA-512 antibodies			0.9567
Positive	97 (52.4)	97 (52.1)	
Negative	88 (47.5)	89 (47.8)	
Micro IAA			0.0551
Positive	39 (29.3)	28 (19.4)	
Negative	94 (70.6)	116 (80.5)	
HbA_{1c} (%)	5.35 ± 0.39	5.33 ± 0.34	0.5949
C-peptide area under curve			
During intravenous glucose tolerance test	34.8 (15.6)	35.1 (16.7)	0.8800
During oral glucose tolerance test	502.5 (201.1)	502.1 (207.2)	0.9858
During mixed meal tolerance test	383.1 (172.4)	381.0 (183.8)	0.9102

Data are means ±SD, *n* (%), or mean (interquartile range).

Laboratory measures

All assays were performed as previously described (1), including ICA (indirect immunofluorescence), IAA (competitive fluid-phase radioassay), plasma glucose (glucose oxidase method), insulin (radioimmunoassay), C-peptide (radioimmunoassay), and HLA-DQ typing (PCR using sequence-specific probes).

Statistical methods

The trial was designed assuming a 5-year cumulative diabetes incidence of 26–50% (annual hazard rate 6%), 80% power to detect a 50% reduction in incidence in the oral insulin group, and $\alpha = 0.05$ (two-tailed). The oral insulin trial was designed to accrue subjects for 4 years with 2 years of follow-up and an annual rate of loss to follow-up of 10%, yielding an estimated average planned duration of treatment of 2.8 years with a projected 70 events occurring. The original projection was for a 4-year accrual period and sample size of 490 subjects in the oral insulin trial.

Variables not normally distributed were log-transformed for analysis and back-transformed for presentation. Data were analyzed according to the intention-to-treat principle. Kaplan-Meier life tables were constructed and compared by the log-rank χ^2 statistic. Categorical variables were compared by Pearson's χ^2 test or Fisher's exact test. Differences in means were tested using ANOVA. Tests of significance were two-tailed. Statistical analyses were performed using SAS software. Data on safety and efficacy were evaluated twice yearly by an independent Data Safety Monitoring Board, with predefined stopping rules.

RESULTS — Screening began on 15 February 1994, and the first subject in this protocol was randomly assigned on 10 September 1996. The actual enrollment period was 6.1 years. By the time randomization was completed (31 October 2002), screening samples for ICA had been obtained from 103,391 relatives. Of these, 97,634 were eligible for further study. Ineligible samples came from individuals without an identified relative with diabetes or not in the age range defined by the protocol. By the end of enrollment, 97,273 samples were analyzed for ICA and 3,483 (3.58%) relatives were ICA positive. Of these, 458 (13.1% of ICA^+ individuals) were excluded before randomization because they already had diabetes. A total of 2,523 (72.4% of ICA^+ individuals) underwent staging. There were 1,844 relatives with intravenous glucose tolerance FPIR above threshold. As staging continued, a total of 388 relatives were classified as intermediate risk and eligible for randomization; of these, 372 were randomized (97% of eligible subjects), 186 to each study arm (Fig. 1). Table 1 shows baseline characteristics; there were no statistically significant differences between treatment groups. Online appendix Fig. 1 (available at http://care.diabetesjournals.org) shows the frequency distribution of age at randomization by treatment arm.

Participants were followed for a median of 1,582 days (4.3 years; interquartile range 928-1988). Annual rate of loss to follow-up was 0.2%, less than anticipated in the protocol (10%). Annual noncompliance rate was 3.7% in the oral insulin group and 6.6% in the placebo group, with noncompliance being failure to attend for scheduled tests and/or failure to take study medication.

Final primary end point data were available for 98.4% of subjects randomized. Diabetes was diagnosed in 97 participants—44 in the oral insulin group and 53 in the placebo group. The majority (72%) of participants were asymptomatic at the time of diagnosis and/or were detected by study OGT tests. The proportion of participants who developed diabetes, averaged annually over follow-up, was 6.4% per year in the oral insulin group and 8.2% per year in the placebo group. Cumulative incidence of diabetes

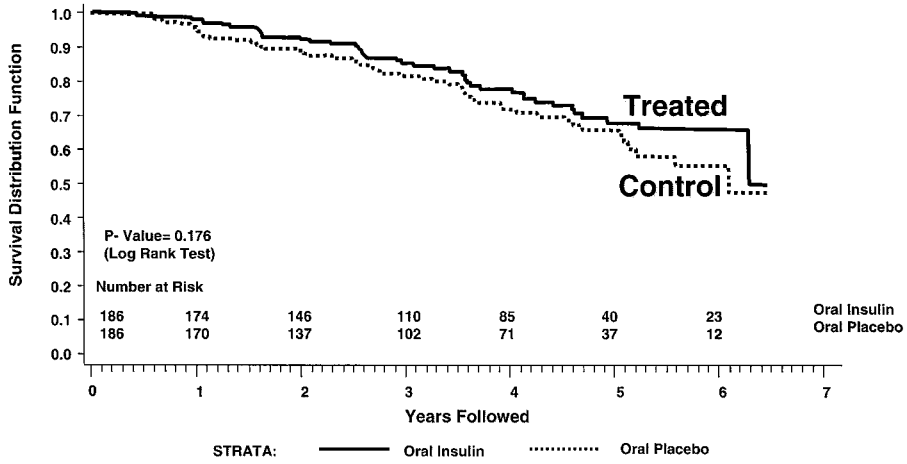

Figure 2—*Kaplan-Meier curves showing the proportion of subjects without diabetes during the trial, by treatment assignment. The number of subjects at risk in each group at each year of follow-up is enumerated at the bottom of the figure. The log-rank test was used for comparison between the groups, with the* P *values as indicated.*

was similar in both groups (hazard ratio 0.764, 95% CI 0.511–1.142, $P = 0.189$) (Fig. 2).

Progression to suspected diabetes (diabetes on one occasion not subsequently confirmed) and progression to first abnormal OGT test were examined separately (online appendix Fig. 2*A* and *B*). No treatment differences were found. Time to FPIR below threshold was also examined and again no difference was found (online appendix Fig. 2*C*).

Insulin secretion was examined before diagnosis of diabetes by assessing the C-peptide response during OGT and mixed-meal tolerance tests. There was no difference between groups for peak C-peptide value or area under the curve. Online appendix Fig. 3 shows area under the curve C-peptide values during OGT tests.

There was no difference in glycemia between groups in the intention-to-treat analysis. A secondary regression analysis revealed that, compared with those who did not develop diabetes, subjects who progressed to diabetes had a slight progressive increase in both HbA_{1c} ($P < 0.001$) and area under the curve glucose on serial OGT tests ($P < 0.001$).

There were no serious adverse events and no differences between groups in frequency of adverse events. Rate of chemical hypoglycemia, assessed without ascertainment bias, was 4.4 per 100 patient-years in the oral insulin group and 3.4 per 100 patient-years in the placebo group ($P = 0.387$). There were no reported episodes of severe hypoglycemia.

As noted, the initial entry criterion for IAA was a level ≥80 nU/ml, which was subsequently changed to a level ≥39 nU/ml. There was the suggestion of an increased rate of progression to diabetes in subjects with IAA values ≥80 nU/ml (confirmed on two occasions; $n = 263$) compared with those with IAA values not confirmed ≥80 nU/ml (in which at least one or both measurements were 39–79 nU/ml; $n = 109$; $P = 0.052$) (Fig. 3). Table 2 shows baseline characteristics in those two cohorts; subjects with confirmed IAA values ≥80 nU/ml were younger and more likely to be male and had higher ICA titers, higher frequency of other autoantibodies, and lower levels of C-peptide. All of these characteristics are consistent with higher risk of diabetes.

Among participants with confirmed IAA ≥80 nU/ml ($n = 263$), the proportion who developed diabetes was 6.2% per year in the oral insulin group and 10.4% per year in the placebo group, averaged annually over follow-up (hazard ratio 0.566, 95% CI 0.361–0.888; $P = 0.015$) (Fig. 4). From the data, the delay in diabetes, calculated from median survival times, is projected as 4.5 years. Online appendix Table 1 shows baseline characteristics of this cohort; except for greater proportion of males in the oral insulin group, there were no statistically significant differences between treatment groups.

In contrast, among participants not confirmed as IAA ≥80 nU/ml ($n = 109$), the proportion who developed diabetes was 6.9% per year in the oral insulin group and 2.7% per year in the placebo group, averaged annually over follow-up (hazard ratio 2.702; 95% CI 0.949–7.694; $P = 0.079$; online appendix Fig. 4). Online appendix Table 2 shows baseline characteristics; there were no statistically significant differences between the oral insulin and placebo groups.

In an analysis confined to subjects randomized before the change in IAA criterion on 31 October 1997 ($n = 106$), all of whom had confirmed IAA ≥80 nU/ml, the proportion who developed diabetes was 6.4% per year in the oral insulin

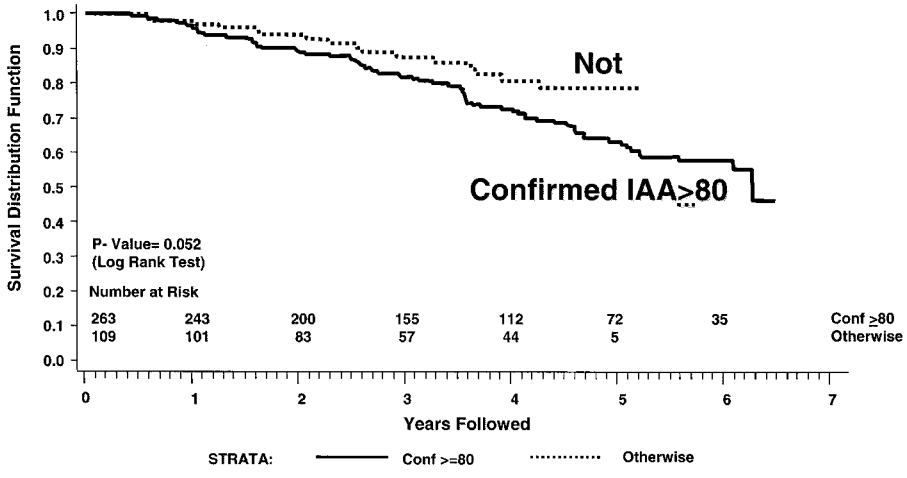

Figure 3—*Kaplan-Meier curves showing the proportion of subjects without diabetes during the trial by baseline IAA level (confirmed value ≥80 nU/ml vs. at least one value 39–79). The number of subjects at risk in each group at each year of follow-up is enumerated at the bottom of the figure. The log-rank test was used for comparison between the groups, with the* P *values as indicated.*

Table 2—*Baseline characteristics of subjects by IAA status*

	Not confirmed IAA ≥80	Confirmed IAA ≥80	*P* value
n	109	263	
Median age	13.0 (9–18)	9.0 (6–12)	0.0000
Average FPIR (μU/ml) (SD)	172.1 ± 73.1	155.3 ± 91.4	0.0878
Race			0.9246
White	96 (88.0)	231 (87.8)	
African American	2 (1.8)	5 (1.9)	
Hispanic	7 (6.4)	15 (5.7)	
Other	4 (3.6)	12 (4.5)	
Sex			0.0445
Male	57 (52.2)	167 (63.5)	
Female	52 (47.7)	96 (36.5)	
Relationship to index patient with diabetes			0.1649
Sibling	58 (53.2)	162 (61.6)	
Offspring	31 (28.4)	71 (27.0)	
Parent	9 (8.2)	9 (3.4)	
Second degree	11 (10.0)	21 (7.9)	
Antibody levels			
Median ICAs (JDF units)	40 (20–160)	80 (40–320)	0.0001
Mean IAAs (nU/ml)	72.0 ± 72.3	485.2 ± 547.5	0.0000
GAD antibodies			0.0461
Positive	74 (68.5)	206 (78.3)	
Negative	34 (31.4)	57 (21.6)	
ICA-512 antibodies			0.0043
Positive	44 (40.7)	150 (57.0)	
Negative	64 (59.2)	113 (42.9)	
Micro IAA			0.0000
Positive	4 (5.0)	63 (31.9)	
Negative	76 (95.0)	134 (68.0)	
HbA_{1c} (%)	5.33 ± 0.37	5.35 ± 0.36	0.6112
C-peptide area under curve			
During intravenous glucose tolerance test	40.1 (16.7)	32.8 (15.4)	0.0001
During oral glucose tolerance test	563.9 (225.0)	476.6 (189.1)	0.0002
During mixed-meal tolerance test	443.2 (183.3)	365.2 (169.5)	0.0000

Data are means ± SD, *n* (%), or mean (interquartile range).

group and 11.3% per year in the placebo group, averaged annually over follow-up (hazard ratio 0.539; 95% CI 0.298–0.976; $P = 0.035$) (Fig. 5). From the data, the delay in diabetes, calculated from median survival times, is projected as 4.8 years. Online appendix Table 3 shows baseline characteristics; there were no statistically significant differences by treatment.

CONCLUSIONS — Oral insulin has been used in three studies to test the concept of oral antigen administration in an effort to preserve pancreatic islet β-cell function in newly diagnosed type 1 diabetes (20–22). All three trials failed to show a consistent beneficial effect. Likewise, in BB rats, oral insulin not only failed to prevent type 1 diabetes (23) but, when administered with an adjuvant, actually accelerated the development of diabetes (24). This finding is in stark contrast with the beneficial effects of oral insulin observed in the nonobese diabetic mouse (8–13) and in a transgenic mouse model of virus-induced diabetes (14). Oral antigen administration had only small and inconsistent benefits in clinical trials in multiple sclerosis and rheumatoid arthritis, despite success in animal models of those autoimmune diseases.

Unfortunately, in the primary analysis of relatives selected and randomized in DPT-1, oral insulin did not delay or prevent development of diabetes. There was greater variability in the IAA assay for values 39–79 nU/ml than for values ≥80 nU/ml, particularly in confirmation of a positive result (98.7% overall confirmation for values ≥80 nU/ml compared with 70.6% for values 39–79 nU/ml). This prompted comparison of the rate of evolution of diabetes by entry IAA level (Fig. 3). The cohort with confirmed IAA ≥80 nU/ml (the original entry IAA criterion) progressed to diabetes at a faster rate than those subjects who did not have confirmed IAA ≥80 nU/ml. In addition, those with confirmed IAA ≥80 nU/ml had other risk characteristics that suggest more rapid evolution to diabetes, including younger age, greater likelihood of having other antibodies, and greater loss of β-cell function (lower levels of plasma C-peptide in response to several provocative challenges).

We then examined the effects of intervention in each of these two subgroups. The group with confirmed IAA ≥80 nU/ml showed a beneficial effect of oral insulin, whereas the group who did not have confirmed IAA ≥80 nU/ml showed a trend suggesting a detrimental effect of oral insulin. This group also had a much lower overall rate of development of diabetes. Thus, the significance of this finding is unclear but is reminiscent of the adjuvant induced acceleration of diabetes observed in the BB rat (24).

To gain further insight into the impact of the change that was made in the entry IAA criterion, we performed an analysis confined to subjects randomized before the change in IAA criterion (31 October 1997), all of whom had confirmed IAA ≥80 nU/ml. In this analysis, the results were comparable to those seen in all subjects with confirmed IAA ≥80 nU/ml. There is an obvious lesson for clinical trialists not to tamper with the trial design because enrollment is lagging. One might hypothesize that there might have been a clear beneficial result in the overall trial if the IAA entry criterion had not been changed. However, because none of these subgroup analyses were prespecified, the results suggesting a potential beneficial effect in the subgroup with baseline-confirmed IAA ≥80 nU/ml (either all subjects or those enrolled before the protocol change) can only be deemed hypothesis-generating and not a positive outcome. As a consequence, the successor study group to DPT-1, the Type 1 Diabetes TrialNet clinical trials network, is contemplating a confirmatory study to explore the potential role of oral insulin in delaying or preventing type 1 diabetes in relatives found

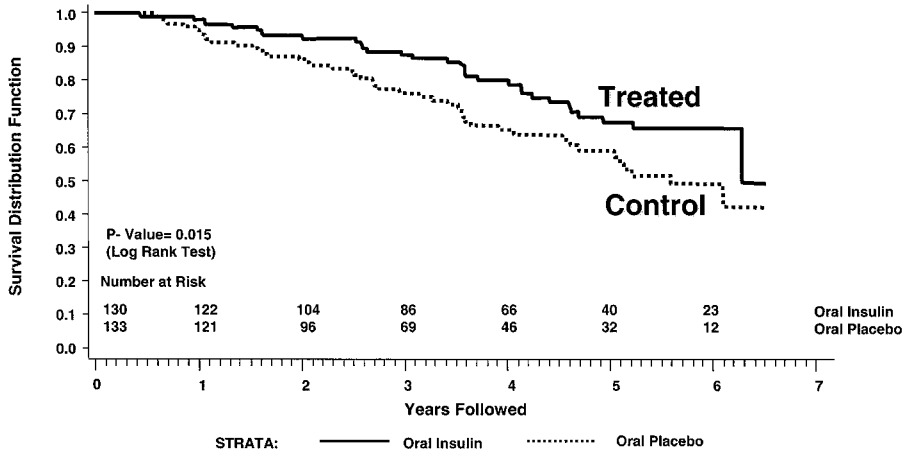

Figure 4—*Kaplan-Meier curves showing the proportion of subjects without diabetes during the trial by treatment assignment for subjects with baseline confirmed IAA ≥80 nU/ml. The number of subjects at risk in each group at each year of follow-up is enumerated at the bottom of the figure. The log-rank test was used for comparison between the groups, with the* P *values as indicated.*

to be at risk for diabetes with IAA levels similar to those in the DPT-1 subgroup.

There are several possible explanations for failure to demonstrate efficacy in the primary analysis. One is that oral insulin has no effect. Another is that inclusion of subjects with variable and lower risk of diabetes (those with IAA 39–79 nU/ml) may have masked a treatment effect or that in some of these subjects diabetes may have been accelerated. A third possibility is that the dose used in this study was unable to sufficiently stimulate the immune system, but this is difficult to test because we have no established immunologic biomarkers of disease progression. Perhaps if an adjuvant had been used, some effect would have been more evident. In animal models that tested oral insulin, heterologous (either porcine or human) insulin was used. It is possible that homologous insulin, as used here, may have failed to elicit a protective immunologic response. Lastly, the timing of our intervention may have been incorrect. Although there has been speculation that once the immunologic markers used to detect relatives at increased risk for type 1 diabetes are detectable then the destructive immune response may be irreversible by an antigen-based therapy, it is of interest that the subgroup who may have had some benefit of therapy had evidence of being farther along in the disease process (higher antibody levels, greater number of antibodies, and lower levels of C-peptide).

The parameters used to predict development of diabetes in relatives of individuals with diabetes were accurate. Risk was projected to be 26–50%, whereas actual risk was 35% over 5 years. Similarly, in our previously reported parenteral insulin trial, 5-year risk was projected to be >50% and actual risk was 65% (1). The ability to quantify risk in relatives of patients with type 1 diabetes and to randomly assign those relatives in controlled clinical trials permits the design of studies that will ultimately lead to determination of whether the type 1 diabetes disease process can be altered in human beings to delay or prevent the development of clinical diabetes.

Three large randomized controlled trials designed to delay or prevent type 1 diabetes—the two DPT-1 trials and the European Diabetes Nicotinamide Intervention Trial (25)—have failed to demonstrate a treatment effect. It should be noted that of the myriad of interventions that had shown preclinical efficacy, both DPT-1 and the European Diabetes Nicotinamide Intervention Trial chose to use interventions with low toxicity in their attempts to interdict the type 1 diabetes disease process. Thus, it should not be concluded that it is impossible to delay or prevent type 1 diabetes; rather, it may require testing of more potent interventions or combinations of therapies, guided by better understanding of the immunopathogenesis of the disease, to demonstrate attenuation or amelioration of the destructive immune process leading to type 1 diabetes.

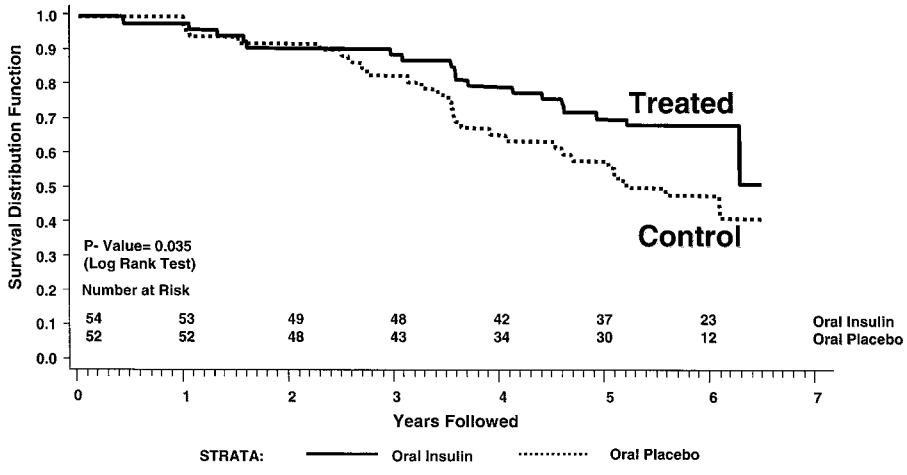

Figure 5—*Kaplan-Meier curves showing the proportion of subjects without diabetes during the trial by treatment assignment for subjects enrolled before protocol change in entry criterion. The number of subjects at risk in each group at each year of follow-up is enumerated at the bottom of the figure. The log-rank test was used for comparison between the groups, with the* P *values as indicated.*

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George S. Eisenbarth, MD, PhD, a member of the DPT-1 Steering Committee, is an inventor of a patent for the use of oral insulin in inducing immunological tolerance in the prevention or treatment of type 1 diabetes.

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APPENDIX

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A complete listing of the DPT-1 Study Group appears in the online appendix. The DPT-1 Protocol and the DPT-1 Manual of Operations are available from the DPT-1 Operations Coordinating Center, University of Miami, 1450 NW 10th Ave., Suite 3054, Miami, FL 33136.

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