Published in final edited form as:

J Pediatr. 2007 January ; 150(1): 31–36.e6.

Pre-Type 1 Diabetes Dysmetabolism: Maximal sensitivity achieved with Both Oral and Intravenous Glucose Tolerance Testing

Jennifer M. Barker, MD¹, Kim McFann, PhD¹, Leonard C. Harrison, MD, DSc², Spiros Fourlanos, MD², Jeffrey Krischer, PhD³, David Cuthbertson, MS³, H. Peter Chase, MD¹, George S. Eisenbarth, MD, PhD¹, and the DPT-1 Study Group*

¹ The Barbara Davis Center for Childhood Diabetes University of Colorado Health Sciences Center Denver Colorado USA

² Autoimmunity and Transplant Division, Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, Australia, 3050

³ Department of Pediatrics University of South Florida, Tampa, FL, USA

Abstract

Objective—To determine the relationship of intravenous (IVGTT) and oral (OGTT) glucose tolerance tests abnormalities to diabetes development in a high-risk pre-diabetic cohort and identify an optimal testing strategy for detecting pre-clinical diabetes.

Study design—Diabetes Prevention Trial Type 1 randomized subjects to oral (n=372) and parenteral (n=339) insulin prevention trials. Subjects were followed with IVGTTs and OGTTs. Factors associated with progression to diabetes were evaluated.

Results—Survival analysis revealed that higher quartiles of 2-hour glucose and lower quartiles of FPIR at baseline were associated with decreased diabetes-free survival. Cox proportional hazards modeling showed that baseline BMI, FPIR and 2-hour glucose levels were significantly associated with an increased hazard for diabetes. On testing performed within 6 months of diabetes diagnosis, 3% (1/32) had normal first phase insulin response (FPIR) and normal 2-hour glucose on OGTT. The sensitivities for impaired glucose tolerance (IGT) and low FPIR performed within 6 months of diabetes diagnosis were equivalent (76% vs. 73%).

Conclusions—Most (97%) subjects had abnormal IVGTTs and/or OGTTs prior to the development of diabetes. The highest sensitivity is achieved using both tests.

Keywords

type 1 diabetes; Diabetes Prevention Trial Type 1 (DPT); oral glucose tolerance test; intravenous glucose tolerance test

Corresponding author: Jennifer M. Barker MD, Barbara Davis Center for Childhood Diabetes, University of Colorado Health Sciences Center, 4200 E. 9th Avenue B140, Denver CO 80262.

* List of the members of the Diabetes Prevention Trial—Type 1 Diabetes (DPT-1) Study Group is available at www.jpeds.com.

NIH AI 39213, DK32083. Dr. Barker is supported by JDRF 11-2005-15. The authors wish to acknowledge the General Clinical Research Center for their contribution RR00051 and RR00069.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

A growing body of evidence supports the hypothesis that type 1 diabetes (T1D) is a chronic autoimmune disease. The autoimmune process is marked by the production of autoantibodies against the pancreatic islet (1–4). Prospective studies of individuals at risk for T1D have shown that subjects can express diabetes associated autoantibodies for years prior to the diagnosis of diabetes (5–9). The metabolic abnormalities of the pre-diabetic period are less well understood. The intravenous glucose tolerance test (IVGTT) has been used as a measure of insulin secretion and abnormalities of the IVGTT such as a diminished first phase insulin response (FPIR) are known to be risk factors for T1D (10–12). Abnormalities of the oral glucose tolerance test (OGTT) have also been shown to precede the diagnosis of T1D (13,14). Both OGTT and IVGTT may be affected by insulin resistance and by pancreatic insulin secretion (15).

The Diabetes Prevention Trial- Type 1 (DPT-1) oral and parenteral insulin prevention trials (16) followed 258 subjects who developed diabetes and an additional 453 who were diabetes-free by the end of the study with serial IVGTTs and OGTTs. The prospective study design and serial testing allow the investigation of the metabolic abnormalities of the pre-diabetic period and the comparison of the ability of these tests to identify individuals at high risk for diabetes.

Methods

Subjects

First and second-degree relatives of patients with T1D were invited to be screened for ICA autoantibodies. Those with ICA >10 JDF units were invited to participate in staging. Staging included confirmation of ICA, measurement of insulin autoantibodies, HLA genotyping, IVGTT and OGTT. Subjects were then diagnosed with diabetes, found to be autoantibody negative or invited to participate in the prevention trials.

Entry criteria into the parenteral arm were set to achieve an approximately 50% five year risk for the development of diabetes (16) and included positive ICA autoantibodies and low first phase insulin response (FPIR) on IVGTT and/or abnormalities in the OGTT other than diabetes. Low FPIR was defined at the 10th percentile for offspring, siblings and second degree relatives (age < 8 years < 60 μ U/mL; age $\geq$ 8 years of age < 100 μ U/mL), or less than the 1st percentile in parents (< 60 μ U/mL). Abnormalities of OGTT included impaired glucose tolerance (IGT) with 2 hour glucose on OGTT $\geq$ 140 mg/dL and < 200 mg/dL and impaired fasting glucose (IFG) with fasting glucose $\geq$ 110 mg/dL and < 126 mg/dL, subjects could have IGT, IFG or both.

Individuals were eligible for the oral trial if they were determined to be ICA and insulin autoantibody positive and had a fasting glucose < 110 mg/dL, a 2-hour glucose of <140 mg/dL on OGTT and a normal FPIR. These subjects had an estimated 5-year risk for T1D of 26–50%. Subjects provided informed consent for participation in these trials and the participating centers' Institutional Review Boards approved the protocols.

Intravenous glucose tolerance testing (IVGTT)

IVGTT was performed as recommended by the ICARUS study group (17) at entry and then at years 2, 4, 6 and at the end of the study. For three days prior to the test, subjects ingested at least 150 grams of carbohydrate. They were fasting for 10 hours and the test was performed prior to 10 AM. Dextrose was administered at a dose of 0.5 gram/kg (maximum 35 grams) intravenously over a 3-minute period. Blood samples were obtained at 4 and 10 minutes prior to and at 1, 3, 5, 7 and 10 minutes after the administration of dextrose and analyzed for glucose and insulin. First phase insulin response (FPIR) was determined as the sum of the 1 and 3 minute insulin levels. The homeostatic model assessment (HOMA-R) was calculated [fasting insulin (mU/l) X fasting glucose (mmol/L)/22.5]. Fasting insulin at the first visit was available

for HOMA-R calculation in 202 subjects in the Oral Trial and 97 subjects in the Parenteral Trial (18).

Oral glucose tolerance testing (OGTT)

OGTT was performed at 6-month intervals. Subjects ingested 1.75 gram/kg of oral glucose (maximum dose 75 grams). Blood samples were obtained for plasma glucose at baseline prior to administration of oral glucose and 30, 60, 90 and 120 minutes later.

Diabetes was diagnosed using American Diabetes Association Criteria including abnormalities of OGTT (fasting glucose ≥ 126 mg/dL and/or if 2 hour glucose ≥ 200 mg/dL) confirmed by a second test obtained within 2 months, symptoms of hyperglycemia and random blood glucose ≥ 200 mg/dL confirmed on a second test, or unequivocal metabolic decompensation with diabetic ketoacidosis. Results were only made available to subjects and researchers if diabetes was diagnosed.

Statistical analysis

Subjects included in this report are all who were randomized to the parenteral or oral insulin prevention trials. Descriptive characteristics are reported as median (interquartile range). Time to diabetes was related to the quartile of glucose (fasting and 2 hour), HOMA-R, FPIR and the ratio HOMA-R:FPIR at the first sampling by Kaplan-Meier survival analysis. The log-rank test was performed to evaluate differences between survival curves. The parenteral and oral insulin trials were analyzed separately. Quartiles of HOMA-R:FPIR at first evaluation were related to diabetes free survival in the oral insulin prevention trial only, as these subjects had normal FPIR at entry. Correlation of metabolic parameters over time to diabetes was performed for glucose (fasting and 2 hour), HOMA-R and FPIR using all tests for all subjects who developed diabetes. Sensitivity and specificity for abnormalities of the OGTT and IVGTT were calculated at intervals prior to the diagnosis of diabetes. If a subject had more than one test performed within the interval, the one closest to the end of the study was chosen.

Cox proportional hazards modeling was used to identify factors in the IVGTT and OGTT performed at the first visit that were related to time to diabetes and the oral and parenteral trials were analyzed separately. Variables included in the models were gender, BMI Z-score, treatment group, FPIR, and 2hour glucose on OGTT, and HOMA-R. In order to determine if the ratio HOMA-R:FPIR contributed additional information on hazard for diabetes for subjects in the oral trial, an additional model was evaluated including BMI z-score, glucose at 120 minutes, and the natural logarithm of the ratio HOMA-R:FPIR ($\ln(\text{HOMA-R:FPIR})$). This analysis was only performed in the oral trial as these subjects had normal FPIR at entry. Two-tailed alpha less than 0.05 was considered statistically significant.

Results

Table I shows the characteristics of subjects entered into the oral and parenteral insulin prevention trials. There was a statistically significant difference in subject characteristics in these two trials on all variables except for age at diagnosis. Subjects enrolled in the parenteral trial were older, had a shorter follow-up time, and higher glucose levels on baseline OGTT at all time points. By design, they had lower FPIR. Subjects in the oral insulin trial had a higher BMI, fasting insulin and HOMA-R compared with subjects in the parenteral insulin trial. This may be a consequence of the entry criteria into the parenteral trial which included a low FPIR. Subjects with increased BMI and insulin resistance would be expected to have a higher fasting insulin and FPIR, and therefore may not meet the entry criteria for the parenteral insulin trial.

Values for FPIR, fasting and 2-hour glucose on OGTT are shown in Table II (available at www.jpeds.com) comparing subjects who did and did not develop diabetes in the oral and parenteral insulin prevention trials.

Survival analyses for glucose quartiles (fasting and 2 hour), FPIR and HOMA-R at first measurement of OGTT and IVGTT in the oral and parenteral trials are summarized in Figure 1. In the oral trial, diabetes free survival was significantly shorter in subjects with higher 2-hour glucose quartiles (diabetes free survival at 5-years quartile 1: 82% (95% confidence interval (CI) 70–90%) vs. quartile 4: 51% (95% CI 37–64%), $p=0.0006$ (Figure 1, A)). In the parenteral trial, higher quartiles of fasting glucose (diabetes free survival at 5 years 43% (95% CI 27–58%) in quartile 1 vs. 29% (95% CI 16–43%) in quartile 4, $p=0.01$) and 2-hour glucose were associated with shorter times to diabetes (diabetes free survival at 5-years quartile 1: 56% (95% CI 40–69%) vs. quartile 4: 28% (95% CI 9–33%), $p<0.0001$ (Figure 1, B)). Additionally, lower quartiles of FPIR were associated with shorter diabetes free survival in the parenteral group (diabetes free survival at 5 years quartile 1: 16% (95% CI 8–27%) vs. quartile 4: 50% (95% CI 35–63%), $p<0.0001$ (Figure 1, C)). Higher ratios of HOMA-R: FPIR were associated with decreased diabetes free survival in the oral trial (diabetes free survival in quartile 1: 88% (95% CI 72–96%) at 5 years and quartile 4: 63% (95% CI 43–78%), $p = 0.0004$). There was no difference in survival curves by quartiles in the oral trial for FPIR ($p=0.41$), fasting glucose ($p=0.68$), HOMA-R ($p=0.59$), or HOMA-R in the parenteral trial ($p=0.47$) data not shown.

Cox proportional hazards modeling was performed (Table III) on OGTT and IVGTT performed at entry to the study. The oral and the parenteral trials were analyzed separately. In the oral trial, baseline BMI z-score, FPIR and 2-hour glucose on OGTT were associated with time to diabetes. For each 1 mg/dL increase in 2-hour glucose, the hazard for diabetes increased by 1.6% ($p<0.0001$) and for each $\mu\text{U/mL}$ decrease in FPIR, the hazard for diabetes increased by 8% in the oral trial ($p=0.023$). In the parenteral trial, FPIR, 2-hour glucose on the OGTT and HOMA-R were significantly related to the time to diabetes. In the parenteral trial, for each 1 mg/dL increase in 2-hour glucose, the hazard for diabetes increased by 0.4% ($p=0.01$) and for each $\mu\text{U/mL}$ decrease in FPIR the hazard for diabetes increased by 10% ($p=0.008$).

Additional models were performed on subjects in the oral trial to evaluate if there was an effect on diabetes hazard of HOMA-R:FPIR independent of FPIR. HOMA-R:FPIR was log-transformed ($\ln(\text{HOMA-R:FPIR})$) for Cox Proportional Hazards analysis. Because of significant collinearity of the variables FPIR, HOMA-R and the ratio HOMA-R:FPIR, they were not included in the same model and an additional model was developed including BMI z-score, 2-hour glucose on OGTT and $\ln(\text{HOMA-R:FPIR})$. All variables were significantly associated with hazard for diabetes with BMI z-score HR = 1.342 (95% confidence intervals (CI) 1.052–1.712, $p=0.02$), 2-hour glucose on OGTT HR = 1.018 (95% CI 1.010–1.025, $p<0.0001$) and $\ln(\text{HOMA-R:FPIR})$ HR = 3.451 (95% CI 1.657–7.185, $p=0.0009$).

In order to evaluate the change in metabolic variables over time, all measurements for all subjects of FPIR, fasting glucose and 2-hour glucose were included and shown in Figure 2. FPIR decreased over time to diabetes ($R=-0.20$, $p<0.0001$) while fasting ($R=0.13$, $p<0.0001$) and 2-hour glucose increased ($R = 0.39$, $p < 0.0001$).

Table IV (available at www.jpeds.com) shows the sensitivity and specificity of abnormalities of fasting plasma glucose, two-hour glucose on oral glucose tolerance testing and FPIR for the development of diabetes. Abnormalities of fasting glucose were a very insensitive predictor of diabetes, 12% were abnormal at less than 6 months prior to the diagnosis. In contrast, abnormalities of FPIR and 2-hour glucose on OGTT had similar sensitivities in the less than 6-month time period, 76% (95% CI 67–83%) for 2-hour glucose and 73% (95% CI 60–83%)

for FPIR. Abnormalities of the OGTT were more specific than abnormalities of FPIR in all time periods prior to the end of the study.

Thirty-two subjects had both IVGTT and OGTT performed within 6 months of the diagnosis of diabetes. Seventeen subjects had elevated 2 hour glucose on OGTT and an FPIR less than the 10th percentile. Only one of the thirty-two subjects (3%) had normal FPIR and 2 hour glucose on OGTT within 6 months of the diagnosis of diabetes. However, 8 subjects (25%) had 2-hour glucose less than 140 mg/dL and 8 subjects had a FPIR greater than the 10th percentile for age within 6 months of the diagnosis of diabetes.

Discussion

The chronic component of progression to T1D has been demonstrated by the production of autoantibodies for years prior to the diagnosis of diabetes (5–9). Through studies such as DPT-1, a clearer picture of the pattern of metabolic abnormalities is emerging. It appears that most pre-diabetic subjects have a low FPIR prior to the diagnosis of diabetes. However, lower quartiles of FPIR were only associated with shorter diabetes free survival in the parenteral study. The lack of observation in the oral study may be a consequence of the entry criteria which eliminated any subjects with a low FPIR.

Abnormalities of OGTT precede the diagnosis of T1D. Most subjects have an elevated two hour glucose on OGTT prior to the diagnosis of diabetes and many subjects maintain a normal fasting glucose even at the diagnosis of diabetes (14). In the DPT-1, only one individual (1/32, 3%) maintained normal IVGTT and OGTT within 6 months of the diagnosis of diabetes. We propose that subjects developing T1D develop glucose abnormalities over a period of time, commencing with elevated post-prandial and 2-hour glucose on OGTT and progressing to fasting hyperglycemia as β -cell function continues to decline.

In this group, abnormalities of 2-hour glucose on OGTT and the FPIR in the IVGTT are equally sensitive for the development of diabetes within 2 years of onset of diabetes. However, FPIR <10th percentile for age is much less specific for diabetes, a significant proportion of the subjects who never developed diabetes within 2 years being abnormal on FPIR (as defined by FPIR < 10th percentile for age). As previously observed, the majority of subjects maintain a normal fasting plasma glucose despite developing abnormalities of the two hour glucose (14). This has important implications for T1D prevention trials and suggests that for maximal sensitivity, both IVGTT and OGTT may be required and that fasting glucose alone is insufficient for the prediction of diabetes.

Insulin resistant states such as puberty have been associated with the onset of diabetes (19). Insulin resistance has been shown to be an independent predictor of the development to T1D (20). The accelerator hypothesis links insulin resistance to the development of T1D as an initiator of autoimmunity (21–23). Alternately, the presence of insulin resistance in an individual may hasten the onset of T1D merely by the fact that more insulin is required to maintain euglycemia. In our population, an increased BMI z-score was associated with shorter time to diabetes. HOMA-R was used as a measure of insulin resistance and only in the population with decreased FPIR at entry (the parenteral trial), was HOMA-R significantly related to the time to diabetes (18). We did observe an association with diabetes free survival to quartiles of the ratio of HOMA-R:FPIR in the oral insulin trial, with higher ratios associated with shorter diabetes free survival.

The natural history of the pre-diabetic period in T1D remains an area of intense research. DPT-1 screened approximately 100,000 relatives of patients with T1D for diabetes related autoimmunity to enroll the 711 subjects into the oral and parenteral insulin prevention trials. The large size and longitudinal follow-up provides an ideal opportunity for investigation of

the natural history of the time period from autoimmunity to diabetes in relatives of patients with T1D. DPT-1 enrolled subjects based on the presence of diabetes associated autoimmunity, therefore conclusions regarding the time prior to the development of autoimmunity cannot be made. Additionally, DPT-1 was limited to subjects with a family history of diabetes and extrapolation to the general population may not be valid.

In summary, abnormalities in the 2-hour glucose on OGTT are as sensitive and have better specificity for predicting diabetes in the 6 months prior to diagnosis of diabetes compared with FPIR below the 10th percentile for age. A significant proportion of subjects have normal OGTT (24%) or normal IVGTT (22%) in the 6 months prior to diagnosis of diabetes. However, a very small subset of patients has both test normal within the 6 months of diagnosing diabetes (3%). Therefore, maximal sensitivity is only achieved when both tests are performed. Increased BMI z-score is associated with an increased hazard for diabetes, suggesting that time to diabetes may be influenced by factors that are associated with increased insulin requirements. Further studies of insulin resistance in the population at risk for T1D are required to define its contribution to the development of diabetes.

Acknowledgements

We wish to acknowledge the patients and families who participated in DPT-1, without whom nothing would be possible.

References

1. Lendrum R, Walker G, Gamble DR. Islet-cell antibodies in juvenile diabetes mellitus of recent onset. *Lancet* 1975;7912:880–883. [PubMed: 47533]
2. Bottazzo GF, Dean BM, Gorsuch AN, Cudworth AG, Doniach D. Complement-fixing islet-cell antibodies in type I diabetes: possible monitors of active beta-cell damage. *Lancet* 1980;8170:668–672. [PubMed: 6103089]
3. Verge CF, Stenger D, Bonifacio E, Colman PG, Pilcher C, Bingley PJ, Eisenbarth GS. Combined use of autoantibodies (IA-2 autoantibody, GAD autoantibody, insulin autoantibody, cytoplasmic islet cell antibodies) in type 1 diabetes: Combinatorial Islet Autoantibody Workshop. *Diabetes* 1998;47:1857–1866. [PubMed: 9836516]
4. Yu L, Robles D, Rewers M, Kaur P, Keleman K, Eisenbarth GS. High-throughput insulin autoantibody assay: 96 well filtration plate format. *Diabetes* 1999;48:A213.
5. Gardner SG, Gale EA, Williams AJ, Gillespie KM, Lawrence KE, Bottazzo GF, Bingley PJ. Progression to diabetes in relatives with islet autoantibodies. Is it inevitable? *Diabetes care* 1999;22:2049–2054. [PubMed: 10587841]
6. Bruining GJ, Molenaar JL, Grobbee DE, Hoffman A, Scheffer GJ, Bruining HA, DeBruyn AM, Valkenburg HA. Ten-year follow-up study of islet-cell antibodies and childhood diabetes mellitus. *Lancet* 1989;8647:1100–1103. [PubMed: 2566050]
7. Bingley PJ, Christie MR, Bonifacio E, Bonfanti R, Shattock M, Fonte M-T, Bottazzo G-F, Gale EAM. Combined analysis of autoantibodies improves prediction of IDDM in islet cell antibody-positive relatives. *Diabetes* 1994;43:1304–1310. [PubMed: 7926304]
8. Bingley PJ, Bonifacio E, Williams AJ, Genovese S, Bottazzo GF, Gale EAM. Prediction of IDDM in the general population: strategies based on combinations of autoantibody markers. *Diabetes* 1997;46:1701–1710. [PubMed: 9356015]
9. Verge CF, Gianani R, Kawasaki E, Yu L, Pietropaolo M, Jackson RA, Chase HP, Eisenbarth GS. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 1996;45:926–933. [PubMed: 8666144]
10. Chase HP, Dolan LM, Krischer JP, White N, Wolfsdorf JJ, Cuthbertson DD, Kaufman F, Schatz DA, Wilson DM. The DPT-1 Study Group. First phase insulin release during the intravenous glucose tolerance test as a risk factor for type 1 diabetes. *J Pediatr* 2001;138:244–249. [PubMed: 11174623]

11. Eisenbarth GS, Gianani R, Yu L, Pietropaolo M, Verge CF, Chase HP, et al. Dual parameter model for prediction of type 1 diabetes mellitus. *Proc Assoc Am Physicians* 1998;110:126–135. [PubMed: 9542768]
12. Vardi P, Crisa L, Jackson RA, Herskowitz RD, Wolfsdorf JI, Einhorn D, et al. Predictive value of intravenous glucose tolerance test insulin secretion less than or greater than the first percentile in islet cell antibody positive relatives of type I (insulin-dependent) diabetic patients. *Diabetol* 1991;34:93–102.
13. Rosenbloom AL, Hunt SS, Rosenbloom EK, Maclaren NK. Ten-year prognosis of impaired glucose tolerance in siblings of patients with insulin-dependent diabetes. *Diabetes* 1982;31:385–387. [PubMed: 6759254]
14. Greenbaum CJ, Cuthbertson D, Krischer JP. Type I diabetes manifested solely by 2-h oral glucose tolerance test criteria. *Diabetes* 2001;50:470–476. [PubMed: 11272162]
15. Allen HF, Jeffers BW, Klingensmith GJ, Chase HP. First-phase insulin release in normal children. *J Pediatr* 1993;123:733–738. [PubMed: 8229481]
16. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 2002;346:1685–1691. [PubMed: 12037147]
17. Bingley PJ, Colman P, Eisenbarth GS, Jackson RA, McCulloch DK, Riley WJ, et al. Standardization of IVGTT to predict IDDM. *Diabetes care* 1992;15:1313–1316. [PubMed: 1425095]
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetol* 1985;28:412–419.
19. Greenbaum CJ. Insulin resistance in type 1 diabetes. *Diabetes Metab Res Rev* 2002;18:192–200. [PubMed: 12112937]
20. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between Type I and Type II diabetes. *Diabetol* 2001;44:914–922.
21. Betts P, Mulligan J, Ward P, Smith B, Wilkin T. Increasing body weight predicts the earlier onset of insulin-dependant diabetes in childhood: testing the ‘accelerator hypothesis’. *Diabet Med* 2005;22:144–151. [PubMed: 15660730]
22. Daneman D. Is the ‘Accelerator Hypothesis’ worthy of our attention? *Diabet Med* 2005;22:115–117. [PubMed: 15660726]
23. Fourlanos S, Narendran P, Byrnes GB, Colman PG, Harrison LC. Insulin resistance is a risk factor for progression to type 1 diabetes. *Diabetol* 2004;47:1661–1667.

Appendix

The members of the Diabetes Prevention Trial–Type 1 Diabetes (DPT-1) Study Group are as follows:

Steering Committee: J.S. Skyler (University of Miami, Chair), D. Brown (University of Minnesota), H.P. Chase (University of Colorado), E. Collier (National Institute of Allergy and Infectious Diseases), C. Cowie (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK]), G.S. Eisenbarth (University of Colorado), J. Fradkin (NIDDK), G. Grave (National Institute of Child Health and Human Development), C. Greenbaum (Virginia Mason Research Center), R.A. Jackson (Joslin Diabetes Center), F.R. Kaufman (Children’s Hospital Los Angeles), J.P. Krischer (University of South Florida), J.B. Marks (University of Miami), J.P. Palmer (University of Washington), A. Ricker (Children’s Hospital, Boston), D.A. Schatz (University of Florida), D. Wilson (Stanford University), W.E. Winter (University of Florida), J. Wolfsdorf (Children’s Hospital, Boston), A. Zeidler (University of Southern California);

Previous Members: H. Dickler, R.C. Eastman, N.K. Maclaren, J.I. Malone, and P.R. Robertson;

Writing and Review Committee: J.S. Skyler, J.P. Krischer, J. Wolfsdorf, C. Cowie, J.P. Palmer, C. Greenbaum, D. Cuthbertson (University of South Florida), L.M. Rafkin-Mervis (University of Miami), F.R. Kaufman, and H.P. Chase;

Planning Committee: J.P. Palmer (Chair), H.P. Chase, C. Cowie, J. Fradkin, G.S. Eisenbarth, C. Greenbaum, K. Herold (Columbia University), F.R. Kaufman, J.P. Krischer, J.B. Marks, L. Rafkin-Mervis, D.A. Schatz, J.S. Skyler;

Trial Co-ordinators: B. Aneju (Stanford University), D. Conboy (Joslin Diabetes Center), R. Cook (University of Florida), M.A. Dennis (University of Florida), L. Finney (University of Minnesota), S. Harris (University of Colorado), D. Matheson (University of Miami), M. McCulloch-Olsen (Virginia Mason Research Center), T. Smith (Joslin Diabetes Center), J. Valenzuela (Children's Hospital Los Angeles), N. Vega (University of Southern California);

Data Safety and Quality Monitoring Committee: O.B. Crofford (Melbourne, Ark.), D. DeMets (University of Wisconsin), J.M. Lachin (George Washington University), J. Nerup (University of Copenhagen), A. Rossini (University of Massachusetts), A. Schiffrin (McGill University), M. Steffes (University of Minnesota), A. Tsiatis (North Carolina State University), B. Zinman (University of Toronto).

Affiliates

Affiliates: Akron, Ohio — A. Haider, J. Haas; Albany, N.Y. — R. Busch, K. Marshilok, N. Toleno; Albuquerque, N.M. — D. Schade, P. Katz, D. Hornbeck; Alexandria, La. — S. Foster, W.E. Roberts, M. Vercher; Ann Arbor, Mich. — C. Foster, C. Bower; Atlanta — I.L. Hansen, D. Burcell, S. Anderson, R. Shultz, C. Sparks; Austin, Tex. — J. Wray, L. Goldman, R.M. Holt; Baltimore — D. Counts, D. Ostrowski, L. Plotnick, P. Fechner, C. Donnelly; Baton Rouge, La. — P. Bourgeios, P.R. Prosser, B. Bowden; Billings, Mont. — F. Gunville, C. McClave, P. Heldt; Birmingham, Ala. — F. Ovalle, J.A. Atchison, P. Trull, A. Bottomlee; Bismarck, N.D. — S. Betting, T. Davis, J. Wetzstein; Boise, Idaho — C. Clinkingbeard, J. Davis, T.S. Roosevelt; Bronx, N.Y. — H. Shamoon, H. Duffy; Brooklyn, N.Y. — H. Anhalt, L. Brussard, J.V. Capotorto, P. Sheehan, S.A. Quyyumi, N.D. Cohen, B. Recker, S. Castells, W. Bastian, T.W. AvRuskin, V. Verdia; Buffalo, N.Y. — T. Quattrin, K. Dwigun; Burlington, Vt. — W. Cefalu, N. Clark, L. Tilton; Calgary, Alta. — B. Corenblum, S. Harries, A. Whitty; Camp Hill, Pa. — R. McInroy, S. Smith; Charleston, S.C. — S.M. Willi, L.A. Key, D.S. O'Rear; Charleston, W.Va. — S.R. Grubb, K. Taylor, P. Adams; Chattanooga, Tenn. — M. Reeves, P. Reeves, R. Marshall, E. Tessmann; Chicago Heights, Ill. — A. Dwarakanathan, C. Beebe, I. Weintraub-Yohay, P. O'Donnell; Chicago — B. Rich, J. Imperial, B. Silverman, D. Edidin, S. Goodman, I. Brodsky, L. Brodsky; Cincinnati — D. Klein, L. Dolan, D. Standiford; Cleveland — D. Rogers, C. Switzer; Columbia, Mo. — D.E. Goldstein, D. Eichelberger, A. Smith; Columbus, Ohio — C. Ganong, J. Germak, W.B. Zipf, M. Dyas, J.F. Sotos, C. Young; Corpus Christi, Tex. — W. Riley, S. Salai; Dallas — P. Raskin, J. Marks, M. Alford, R. Sachson, C. Lebowitz; Des Moines, Iowa — J. Cook, J. Stedman, D. Indra; Detroit — J. Gutai, B. Vinuya, M. McGraw-Maly; Duarte, Calif. — W. Feng, C. Williams, C.M. Krygsman, M. Pierce; Durham, N.C. — M. Freemark, J. Litton; Edmonton, Alta. — E.A. Ryan, K. Todd; El Paso, Tex. — D. Aboud, M. Pacillas; Erie, Pa. — J.H. Hines, A.F. Walczak, L.F. Aparicio, D. Harbaugh; Fairbanks, Alaska — M. Bergeson, M. Rozell; Fairfield, Alaska — E. Mahan; Folcroft, Pa. — H. Brooks; Fresno, Calif. — P. Ginier, P. Hensley; Glen Ellyn, Ill. — M. Heymann, B. Johnson, J. Tack; Grand Forks, N.D. — L. Sondrol, T. Hjelle; Grand Rapids, Mich. — D. Perry, J. Albert, L. Flory; Great Falls, Mont. — N.C. Gerrity, C. Naab, J. Heck; Greenville, S.C. — S. Weber, P. Mulhall; Gulfport, Miss. — B.G. Lansden; Halifax, N.S. — E. Cummings, S. Salisbury, C.A. Armour; Hartford, Conn. — S. Ratzan, M. Trahiotis; Hollywood, Fla. — R. Nemery, H. Carney, D. Shorkey; Honolulu — D. Fitz-Patrick, A.M.Y.

Taniguchi; Houston — S. Gunn, K. Copeland, S. McGirk; Idaho Falls, Idaho — J. Liljenquist, C. Fielding, S. Richards, V. Best; Indianapolis — H. Rodriguez, G. Freidenberg, L. Amstutz, C. Weir; Iowa City, Iowa — E. Tsalikian, R. Hoffman, M. Bayless; Kalamazoo, Mich. — J.D. Hare, K. Hare; Kansas City, Kans. — J.L. Kyner, G. Eaks; Kansas City, Mo. — C.P. Howard, W. Moore, B. Woodford, T. Salyer; Kennewick, Wash. — N. Wannarachue, R. Meridith, D. Squires; Kiel, Wis. — D. Deubler; Kingsville, Tex. — H. Bruschetta; Knoxville, Tenn. — D.A. Nickels, C. Dothard, A. Courtney; Laguna Hills, Calif. — A.O. Marcus; Lebanon, N.H. — P.J. Beisswenger, S. Kairys, W. Boyle, A.S. Christiano, R. O'Dell, A. Touchette; Lexington, Ky. — K.M. Thrailkill, D. Karounos, S. Webb, L. Moore, P. Allweiss, F. Anderson; London, Ont. — J.L. Mahon, J. McCallum; Los Angeles — L. Raffel, J. Rotter, A. Verne, M.B. Davidson, G. Keppler; Madera, Calif. — S. Banerjee, M. Simon; Madison, Wis. — M.J. MacDonald, S. Mokrohisky; Manhasset, N.Y. — P.W. Speiser, P. Fort, J. Corrigan; Marquette, Mich. — S. Pelkola; Memphis, Tenn. — A.E. Kitabchi, M. Murphy, H. Lambeth, G. Burghen, P. McGlendon, J. Bondani, P. LeNoye; Milwaukee — R. Alemzadeh, M. Koppen; Mineola, N.Y. — J.A. Canas, M. Lamerson; Minneapolis — M. Spencer, D. Etzwiler, K. Reynolds; Missoula, Mont. — N. Eyler, P. Allen; Mobile, Ala. — B.A. Warner, K.R. Rettig, K.L. Levens, M.R. Davis; Montreal — C. Polychronakos, D. Laforte; Naperville, Ill. — W.P. Zeller, J. McKernan, S. Finn; Nashville — A. Powers, J. Lipps; New Albany, Ind. — S. Raghavan, V. Broadstone, P. Raake, K. Weissberg; New Haven, Conn. — W.V. Tamborlane, P. Gatcomb; New Orleans — L. Blonde, T. Zimmerman, R. Zimmerman, C. Liebel, S. Chalew, A. Vargas, J. Rao, J. Ascani, T. Compton; New York City — B. Cerame, M.D. Harbison, R. Newfield, M. New, M. Wajnrajch, I. Vargas, K. Herold, H. Schachner, G. Feberes, N.K. Maclaren, D. Golub, R. Rappaport, R. McEvoy, N. Thomas, X. Pi-Sunyer, R. Saltiel-Berzin; Newark, N.J. — R. Rappaport, J. Koblish; Oklahoma City — P. Blackett, C. Comp, J. Beck; Omaha, Nebr. — J. Hassing, L. Hahn, J.T. Lane, K. Corley, L. Larson; Orange, Calif. — R. Fiallo-Sharer, P. Lee, A. Cortez, N. Varni, H. Speer; Orlando, Fla. — S. Crockett, W. McDaniel, V. Roberts; Philadelphia — S.A. Weinzimer, P. Cohen, L. Baker, D. De Paul, E. Rebecca; Phoenix, Ariz. — R. Dolinar, M.B. Block, P. Krametbauer; Ponce, P.R. — T. Frazer, G. Veray; Portland, Oreg. — A. Ahmann, S. LaFranchi, P. Jennings, A. Kelleher, M. Kummer, J. Hansen, M.K. Hunter, K. LaMorticella, R. Bergstrom, M. Rigdon; Reno, Nev. — K. Eckert; Renton, Wash. — L.J. Klaff, R. Brazg, J. Springs; Richland, Wash. — B. Wilson, E. Isaacson, H. Kuhn; Richmond, Va. — D. Willis, P. Kaplowitz, K. Genther; Rio Piedras, P.R. — C. Bourdony, A. Rivera; Rochester, Minn. — R. Basu, R. Rizza, P. Whannel, N. Jospe, A. Utzman; Sacramento, Calif. — B. Sheikholisham, C. Hiner; Salt Lake City — D. Hardin, R. Lindsay, M. Swinyard, M. Rallison, L. Jarrett, J. Sirstins; San Antonio, Tex. — K. Pierson, S. Trevino, S. Schwartz, K. Dickens; San Bernardino, Calif. — S. Clark, P. Scroggin, G.R. Greene; San Diego, Calif. — L. Linarelli, E. Camuro, S. Hermosillo, R. Estrada, W. Bailey, J. Fuqua; San Francisco — S.E. Gitelman, M. Fountaine; San Juan, P.R. — G. Colon, L. Gonzalez de Pijem, F. Nieves-Rivera, A. Rivera, R. Perez; Santa Barbara, Calif. — L. Jovanovic, S. Vesterfelt; Santurce, P.R. — C.A. Saenz; Seattle — G. Kletter, K. Pihoker, S. Kearns; Sioux Falls, S.D. — L. Keppen, P. Johnson, E. Krell; Skokie, Ill. — S.C. Duck; Spokane, Wash. — M. Noble, S. Thompson, K. Wilson, P. Malody; Springfield, Ill. — N.G. Soler, L. McCall; Springfield, Mass. — H.F. Allen, G. Roumeliotis; Springfield, Mo. — L. Chase, D. Braden-Moll; St. Louis — N. White, L. Levandoski; St. Petersburg, Fla. — J.I. Malone, J. Steinbrueck; State College, Pa. — J.S. Ulbrecht, N. Lambert, P. Mulhall; Stony Brook, N.Y. — T.A. Wilson, A.H. Lane, A. Smaldone; Sylmar, Calif. — T. Modilevsky; Syracuse, N.Y. — R. Izquierdo, R. Weinstock, S. Mackowiak, K. Brindak; Toronto — D. Wherrett, D. Daneman, K. Pearlman, C. McLellan, A. Rogers; Torrance, Calif. — E. Ipp, C. Mao; Traverse City, Mich. — E.H. Rushovich, I. Thorne; Tulsa, Okla. — D.H. Jelley, D. Greer; Vancouver, B.C. — D. Metzger; Washington, D.C. — A. Austin, A. Glasgow, J. Turek, J. Archer, G. Nunlee-Bland, K. Johnson, J. Harris; White Plains, N.Y. — S. Driedbart, R. Noto, A. Romano, W. Herl; Wichita, Kans. — R. Guthrie, O. Tatpati, A. Brenner; Willmar, Minn. — D. Lippert; Wilmington, Del. — G. Reeves, C. Swenson; Winnipeg, Man. — L. Murphy, H. Dean, L. Berard; Winston-Salem, N.C. — S.S.

Werbel, A. Bell-Farrow; Woodinville, Wash. — R. Mauseth, J. Hanson; Youngstown, Ohio — S.K. Mishr, L. DiCaria, B. Wilson. *Satellites*: Aberdeen, S.D. — C. Wischmeier; Akron, Ohio — M.F. Moosa, R. Levy; Albany, N.Y. — J. Desemone; Albany, Oreg. — L. Bentson; Alexandria, Va. — H.M. Lando; Alton, Ill. — J. Hoelscher; Amarillo, Tex. — W.C. Biggs; Ames, Iowa — R. Carano; Anaheim, Calif. — P. Nostrand; Anchorage, Alaska — C. Esquivel, L. Achee, J. Kelly, P. Nolan; Apple Valley, Calif. — T. Otsuka; Appleton, Wis. — K. Heyrmann; Astoria, Oreg. — N. Autio, K. Gohl; Atherton, Calif. — J. Prendergast; Atlanta — B. Bode, H. Delcher, C.H. Reed; Atlantis, Fla. — M. Mellman; Augusta, Ga. — I.C. Herskowitz, W. Hoffman; Augusta, Me. — M. Naas; Austin, Tex. — S. Dubois, S. Fehrenkamp; Aventura, Fla. — L.B. Chaykin; Bakersfield, Calif. — H. Pershadsingh, H. Shah, V.G. Ettinger; Baltimore — B.J. Reiner, J. McLaughlin, P.A. Levin; Bangor, Me. — A. Boniface; Bassett, Nebr. — H. Leigh; Batavia, N.Y. — G. Ginsberg; Bedford, Ohio — D. Weiss; Belleville, Ill. — M. Rosecan; Bellevue, Wash. — P. Doyle; Bellingham, Wash. — J. McAfee, G. Goldfogel; Bend, Oreg. — J. Henschel; Bennington, Vt. — D.M. Gorson; Bethlehem, Pa. — J. Ramos; Beverly Hills, Calif. — M. Bush; Bismarck, N.D. — K. Martin; Blacksburg, Va. — B. Birch; Bremerton, Wash. — S. Reimer; Bristol, Tenn. — J.D. Neil; Bronx, N.Y. — P. Saenger, J. Dimartino-Nardi; Brooklyn, N.Y. — J.V. Capotorto, P. Sheehan, S.A. Quyyumi, N.D. Cohen; Burbank, Calif. — R. Stein; Burlingame, Calif. — D. Klonoff; Butte, Mont. — J. de Souza, D. McCarthy, J. Salisbury, C. Edstrom; Caguas, P.R. — M.F. William; Caldwell, Idaho — M. Brown; Camp Springs, Md. — R. Vigersky; Canton, Ohio — C.E. Smith, A. Krishna, R. Benson; Castaner, P.R. — F. Murphy; Cedar Rapids, Iowa — C. Pruchno; Chapel Hill, N.C. — M. Davenport; Charlottesville, Va. — W.L. Clarke, M. McDuffie; Cheyenne, Wyo. — G. Melinkovich, V. Bell; Chicago Heights, Ill. — A. Ravanam, W. Will; Clearwater, Fla. — D. Leonard; Cleveland — W. Dahms; Clinton, Mo. — K. Scott; Columbia, S.C. — F. Bowyer; Columbus, Ga. — S.B. Leichter; Concord, Calif. — R. Kaplan, S. Lewis; Coopers Mills, Me. — R. Miller; Corpus Christi, Tex. — M. Upmanyu; Culver City, Calif. — N. Goldberg; Danbury, Conn. — R. Savino; Danville, Ind. — S.M. Wentworth; Danville, Pa. — D.R. Langdon; Davenport, Iowa — C. Weideman; Dayton, Ohio — M. Urban; Detroit — D. Transue, F. Whitehouse, J. Cara; Downey, Calif. — S. Shaw; Drayton, S.C. — W. Price; Dubuque, Iowa — R. Iverson; Duluth, Minn. — M. Slag; Durango, Colo. — J. Hutt; Eau Claire, Wis. — N. McLean, R. Moore; El Paso, Tex. — R. Christenson; Elgin, Ill. — K. Valika; Englewood, Colo. — N. Nayak, C.A. Bloch; Englewood, N.J. — L. Strom; Escondido, Calif. — T.S. Bailey, C.P. Varma; Eugene, Oreg. — D. Calder, M. Bilger; Everett, Wash. — K. Larson, M. Papenhausen; Fairfield, Calif. — Y. Shlesinger; Fargo, N.D. — A. Kenien; Fayetteville, N.C. — E. Wright; Flint, Mich. — M.A. Jabbar; Flushing, N.Y. — D.L. Lorber; Fort Dodge, Iowa — J. Berkett; Fort Smith, Ark. — R.P. Robinson; Fort Wayne, Ind. — A. Kadambi; Framingham, Mass. — W. Sullivan; Fremont, Calif. — E. Meyer; Fresno, Calif. — J.L. Bautista, P.C. Norwood; Ft. Lauderdale, Fla. — E. Biederman, S. Nassberg, L. Goscin, M. Mata, N. Thompson, R.M. Harrell, J. Cabral; Ft. Myers, Fla. — A. Pietri; Ft. Worth, Tex. — C.R. Scott, T.K. Flannery, D.B. Wilson; Gainesville, Fla. — B. Rogers; Glendale, Calif. — M. Campos, M.N. Montero; Gorham, N.H. — B. Beals; Grand Junction, Colo. — D. Mair, A. Long; Grand Rapids, Mich. — R.S. Rood; Green Bay, Wis. — J. Taylor; Greensboro, N.C. — R. Sevier; Greenville, N.C. — G. Harris, M.A. Pfeifer; Hackensack, N.J. — M. Blechman, J. Giangola; Hermitage, Tenn. — R. Creech; Hershey, Pa. — M. Lathrop, A. Dunaif; Hollywood, Fla. — G. Miceli, L. Lewy-Alterbaum, P.S. Jellinger, S.B. Novak, K.M. Gellman, S. Lerman; Honolulu — S. Waxman; Houston — D.J. Hamilton; Huntington, W.Va. — H. Driscoll; Huntsville, Ala. — R. Schneier; Hutchinson, Kans. — J.L. Casey; Indianapolis — P. Boyce, J. Meachum; Irving, Tex. — J. Milburn; Issaquah, Wash. — D. Pomeroy; Jackson, Miss. — G. Moll; Jacksonville, Fla. — K. Macyko, L.A. Fox, N. Mauras; Jersey City, N.J. — P. Ledereich; Juneau, Alaska — D. Novotney; Kalispell, Mont. — C. Gill, B. Rossetto; Kingston, Ont. — R. Houlden; Klamath Falls, Oreg. — P. Heck; La Crosse, Wis. — J. Korducki; La Habra, Calif. — J. Winston, D. Geffner; La Jolla, Calif. — S. Edelman, B. Henry; La Mesa, Calif. — D. Einhorn, R. Fink, E. Gold; Lake Charles, La. — R.W. Calhoun; Lake Jackson,

Tex. — J. Leidlein; Lancaster, Calif. — K. Arul; Lansing, Mich. — D. Henry; Las Vegas — D.L. Donaldson; Lebanon, Oreg. — K. Middlestadt; Lewiston, Idaho — L. Grande-Luke; Lincoln, Nebr. — J. Guest, R. Wermers, B. Bells; Little Rock, Ark. — P. Frindik; Livingston, N.J. — G. Gewirtz; Lompoc, Calif. — C. Blyfeld; Long Beach, Calif. — M. Brakin; Los Angeles — D. Borut, D. Geffner, J. Winston, M. Geffner, M. Rodriguez, V. Gura; Los Gatos, Calif. — C. Shough; Louisville, Ky. — H. Bays, H. Shenouda; Lubbock, Tex. — S. Varma, M.J. Bourgeois; Lufkin, Tex. — L.A. Sloan; Lynchburg, Va. — C.E. Guthrow; Lynwood, Calif. — S. Shaw; Manhattan Beach, Calif. — R. Ruby; Margate, Fla. — B. Motzkin-Kava; Marshalltown, Iowa — D. Jebsen; Marshfield, Wis. — I. Zador, S. Maby; McLean, Va. — F. Crantz; Medford, Oreg. — D. Zietlow; Miami Beach, Fla. — D. Kudzma; Miami, Fla. — E. Levy, E.T. Shapiro, J. Jacobi, J. Pita, W. Abelove, J. Perez-Rodriguez, L. Gonzalez-Mendoza, S. Richton, P. Weissman; Middletown, N.Y. — N. Stein; Midland, Tex. — L. Sherman-Adcock; Milwaukee — D. Fergeson, M. Jacobson, J. Sennett, R. Jain; Minneapolis — D. Etzwiler, R.C. Ramsay; Minot, N.D. — M. Holland; Miramar, Fla. — S. Carrington; Missoula, Mont. — S. Seagraves; Modesto, Calif. — G.M. Yue, J. Downs-Colby; Montebello, Calif. — H. Flores; Montgomery, Ala. — S. Weinrib; Morgantown, W.Va. — E. Jones; Morristown, N.J. — H. Starkman; Mount Vernon, Wash. — D. White; Mountain View, Calif. — L. Doberne, M. Greenfield; Muncie, Ind. — K. Alexander; Napa, Calif. — C. O'Sullivan; Naples, Fla. — R. Duncan; Naranja, Fla. — G. Barandiaran, J. Yunis, L. Nunez, V. Ramos; Nashua, N.H. — E. Holland; Natrona Heights, Pa. — W.R. Balash; Neptune, N.J. — J. Sher; New Brunswick, N.J. — R. Agrin; New Orleans — J. Frentz; New York City — I. Fennoy; Newhall, Calif. — S. Baron; Nipomo, Calif. — J. Door; Norfolk, Va. — A. Vinik; North Las Vegas, Nev. — F. Savery; Oakland, Calif. — F. Gareis, R. Mack, D. Devoe, Y. Fan; Oklahoma City — D. Domek; Olympia, Wash. — D. Kelley; Onalaska, Wis. — T. Roberts; O'Neill, Nebr. — B. Gutshall; Orange, Calif. — I. Madu, R. Poucher; Orlando, Fla. — M. Mengel, P. Desrosiers, R.A. Banks, B. Kopp; Pacific Grove, Calif. — I. Fishman; Pacific Palisades, Calif. — D. Geller, W. Smith; Palm Bay, Fla. — J.A. Duncan; Palm Beach Gardens, Fla. — O. Nyman, M. Vaccarello-Cruz; Parkersburg, W.Va. — F.L. Schwartz; Pasadena, Calif. — O. Olambiwonnu; Paso Robles, Calif. — M. Ortiz; Pembroke Pines, Fla. — S. Freedman; Pendleton, Oreg. — S. Merrill; Peoria, Ill. — J. Wise; Philadelphia — I. Rezvani, D. Doyle, P. Hale, C. Singer-Granick, W. Fore; Phoenix, Ariz. — A. Perelman, R. Clemmons, R. Johnsonbaugh; Pittsburgh — A.R. Gonzalez; Pocatello, Idaho — M. Baker, C. Field, C. Shields, K. Walker; Port Huron, Mich. — S. Reddy, K. Pillote; Port St. Lucie, Fla. — M. Borchelt; Port Townsend, Wash. — D. Bommer; Portland, Oreg. — N. Curosh, D. Karl, B. Phillipson; Poway, Calif. — W.L. Iverson; Princeton, N.J. — A. Krosnick; Providence, R.I. — C.B. Kahn; Puyallup, Wash. — B. Blodgett, N. Iverson, C. Jacobson, M. Haynes, D. Moore, R. Alston, R. Eachempati; Raleigh, N.C. — D. Becker; Rapid City, S.D. — L. Weide; Red Wing, Minn. — M. Decker; Redding, Calif. — J. Greaves; Richburg, S.C. — M.J. Curry; Richmond, Va. — J. Radcliffe; Ridgecrest, Calif. — V. Schauf; Riverside, Calif. — D. Childs; Riverside, Ill. — R. Crawford, G. Charnogursky; Robbinsdale, Minn. — M. Stesin; Rockford, Ill. — M. Schneider; Rockville, Md. — H.W. Rodbard, M.A. Dempsey; Roseau, Minn. — R. Brummer; Roseburg, Oreg. — L. Elston, D. Marseters; Rutland, Vt. — P. Lapp; Sacramento, Calif. — N. Glaser, J.S. Soeldner; Safford, Ariz. — V. Chaurasia; Salem, Oreg. — R. Michaels; Salinas, Calif. — A. King, R. Olson; San Antonio, Tex. — D. Hale, M. Danney, S.S. Miller; San Carlos, Calif. — S. Madan; San Diego, Calif. — J.R. Dudl; San Francisco — N. Bohannon, M. Berlund, T. Jackson; San Jose, Calif. — J. Kitzmiller; Santa Rosa, Calif. — D. Price; Savannah, Ga. — K. Ehsanipoor; Sayre, Pa. — M.R. Homan; Scarborough, Me. — J. Olshan; Scottsbluff, Nebr. — T. Sorensen; Scranton, Pa. — A. Perry; Seattle — G.T. Nepom, D. McCulloch, I. Hirsch, R. Kanter, N. Niles; Shattuck, Okla. — M. Vogiatzi; Sheboygan, Wis. — V. Kerpe; Shreveport, La. — R. McVie; Sioux City, Iowa — J. Aniszewski, T. Carroll, R. Bacon; South Bend, Ind. — M. Hudson, A. Simpson; South Miami, Fla. — M. Fili, D. Krieger; South Windsor, Conn. — D. Golob; Southfield, Mich. — J. Carney; Springfield, Ill. — R. Khardori; St. Cloud, Minn. — M. Peitso; St. Louis — J.T. Lane; St. Paul, Minn. — H. Katz, R. Warhol; Staten Island, N.Y. — J. Rothman;

Stockton, Calif. — D.F. Jensen, J. Rooke; Stoughton, Mass. — H. Fogel, L. Hotes; Sumter, S.C. — U. Lilavivat; Tacoma, Wash. — T. Gauthier; Tallahassee, Fla. — L. Deeb, T. Sherradan; Tarzana, Calif. — N. Lavin; Tecumseh, Nebr. — K. Shuey; Toledo, Ohio — J. Horner; Torrance, Calif. — J.M. Tsao; Traverse City, Mich. — A. Scrogin; Trexlertown, Pa. — C. Greenlee; Tucson, Ariz. — J. Insel, M. Wheeler; Tuscaloosa, Ala. — T. Kamal; Tyler, Tex. — L. Wiertz; Union, N.J. — H. Bucholtz, J. Dunn; Urbana, Ill. — K. Wilson; Valhalla, N.Y. — M. Frey, R. Noto; Ventura, Calif. — R. Chochinov; Vincennes, Ind. — J.M. Bridges; Waco, Tex. — M. Amar; Walnut Creek, Calif. — R. Weinstein, T.E. Poore; Waltham, Mass. — S. Brink, K. Moltz; Washington, D.C. — D. Sobel, G. Francis, R. Sveck, J. Ramey; Waterford, Mich. — N. Haque; Watseka, Ill. — A. Villafria, R.E. Villafria; Wausau, Wis. — J. Madagame; Wenatchee, Wash. — L. Stone; West Carrollton, Ohio — R. Cech; West Yellowstone, Mont. — J. Schnelbach; White Plains, N.Y. — S. Dreidbart, R. Noto, T. Lebinger, L. Shane; Whittier, Calif. — E. Reece, R. Harris, W.D. Welsh; Wilmington, N.C. — P.C. Whitesides; Winter Park, Fla. — A. Scoma; Woodland Hills, Calif. — F.H. Ziel; Worcester, Mass. — C. Alter, P. Lock; Yakima, Wash. — G. Treece.

Abbreviations

T1D	Type 1 diabetes
OGTT	oral glucose tolerance test
IVGTT	intravenous glucose tolerance test
DPT-1	Diabetes prevention trial type 1
FPIR	first phase insulin response

Time to diabetes by quartiles of 2 hour glucose (Oral Trial)

Quartile 2 hour glucose	Number at risk					
1	93	88	73	59	46	22
2	99	86	68	47	35	18
3	95	89	74	59	45	20
4	85	79	64	42	28	14

Time to diabetes by quartiles of 2 hour glucose (Parenteral Trial)

Quartile 2 hour glucose	Number at risk					
1	93	88	73	59	46	22
2	99	86	68	47	35	18
3	95	89	74	59	45	20
4	85	79	64	42	28	14

Time to diabetes by quartiles of FPIR (Parenteral Trial)

Figure 1.

A: Time to diabetes by quartile of 2-hour glucose on oral glucose tolerance testing in the Oral Insulin Prevention Trial. Subjects in the highest quartile of 2-hour glucose had a shorter diabetes free survival time compared with subjects in the lowest quartile, ($p=0.0006$). Quartile 1: 44 mg/dl – 92mg/dL; Quartile 2: 93mg/dL – 108 mg/dL, Quartile 3: 108 mg/dL – 120 mg/dL; Quartile 4: 121 mg/dL – 139 mg/dL.

B: Time to diabetes by quartile of 2-hour glucose on oral glucose tolerance testing in the Parenteral Insulin Prevention Trial. Subjects in the highest quartile of 2-hour glucose had a shorter diabetes free survival time compared with subjects in the lowest quartile ($p<0.0001$). Quartile 1: 40 mg/dl – 102 mg/dL; Quartile 2: 103 mg/dL – 119mg/dL, Quartile 3: 120 mg/dL – 147 mg/dL; Quartile 4: 148mg/dL – 199 mg/dL.

C: Time to diabetes by quartile of first phase insulin response on intravenous glucose tolerance testing in the Parenteral Insulin Prevention Trial. Subjects in the lowest quartile of FPIR had a shorter diabetes free survival time compared with subjects in the highest quartile, ($p<0.0001$). Quartile 1: 8.3 μ U/mL – 52 μ U/mL; Quartile 2: 53 μ U/mL L – 73 μ U/mL, Quartile 3: 74 μ U/mL – 102 μ U/mL; Quartile 4: 103 μ U/mL – 325 μ U/mL.

Figure 2.

A: First phase insulin response over time to diabetes including all subjects who developed diabetes and all intravenous glucose tolerance tests.

B: Fasting glucose over time to diabetes, including all subjects who developed diabetes and all oral glucose tolerance tests.

C: 2-hour glucose over time to diabetes, including all subjects who developed diabetes and all oral glucose tolerance tests.

Table 1

Subject characteristics

	ORAL N=372	PARENTERAL N=339	P
Age at randomization	10.64 (7.11–14.13)	11.93 (8.65–18.14)	<0.0001
Follow-up time	3.56 (2.05–4.85)	2.01 (1.34–4.16)	<0.0001
Age at diabetes	12.33 (9.21–16.34) (N=98)	12.62 (9.77–15.25) (N=160)	0.73
Gender	40% (148) female	48% (163) female	0.03
BMI Z-score	0.48 (−0.18–1.27)	0.07 (−0.67–0.63)	<0.0001
FPIR	134 (99.5–194)	73 (52–102)	<0.0001
Fasting insulin	12.6 (9.0–22.7)	10.5 (7.85–13.5)	0.001
HOMA-R	2.80 (2.01–3.67)	2.30 (1.67–3.21)	0.003
Fasting glucose	85 (79–90.5)	88 (81–94)	<0.0001
Glucose, 30 minute	139 (123–157)	151 (132–170)	<0.0001
Glucose, 60 minute	124 (102–146)	154 (127–183)	<0.0001
Glucose, 90 minute	113 (97.5–129)	135 (110–167)	<0.0001
2-hour glucose	108 (92.5–120)	119.5 (102–147)	<0.0001

Data presented are median and IQ range

Table 2a

FPIR prior to the end of the study by study group and diabetes vs. no diabetes

1 to 2 years prior to the end of the study					
	ORAL STUDY		PARENTERAL STUDY		
	No Diabetes N = 183	Diabetes N = 78	No Diabetes N = 86	Diabetes N = 76	P
FPIR	146 (107–201)	106 (77–149) ^a	93.5 (71–138) ^a	67 (45–93) ^{abc}	<0.0001
2 to 3 years prior to the end of the study					
	No Diabetes N = 185	Diabetes N = 63	No Diabetes N = 82	Diabetes N = 67	
FPIR	146 (105–203)	126 (82–195)	86 (59–131) ^{ab}	70 (43–101) ^{ab}	<0.0001
3 to 4 years prior to the end of the study					
	No Diabetes N = 152	Diabetes N = 50	No Diabetes N = 67	Diabetes N = 49	
FPIR	155 (118–228)	118.5 (87–154) ^a	75 (60–123) ^{ab}	70 (49–162) ^{ab}	<0.0001
4 to 5 years prior to the end of the study					
	No Diabetes N = 120	Diabetes N = 35	No Diabetes N = 62	Diabetes N = 26	
FPIR	145 (114.5–199)	135 (120–207)	84.5 (65–108) ^{ab}	74.5 (53–109) ^{ab}	<0.0001

Data presented as median with IQ range

^a p<0.05, vs. oral study no diabetes^b p<0.05, vs. oral study diabetes^c p<0.05, vs. parenteral study no diabetes

Table 2b

Fasting and 2-hour glucose on OGTT prior to the end of the study by study group and diabetes vs. no diabetes

1 to 2 years prior to the end of the study					
	ORAL STUDY		PARENTERAL STUDY		
	No Diabetes N = 221	Diabetes N = 83	No Diabetes N = 135	Diabetes N = 120	
Fasting glucose	86 (80.5–92)	89 (79–94)	90 (84–91) ^a	93 (87–100) ^{ab}	<0.0001
2-hour glucose	110 (95–125)	128 (112–150) ^a	116 (99–132) ^b	144 (124–171) ^{abc}	<0.0001
2 to 3 years prior to the end of the study					
	No Diabetes N = 200	Diabetes N = 62	No Diabetes N = 126	Diabetes N = 81	
Fasting glucose	87 (81–93)	86 (81–93)	87 (81–93)	90 (82–96)	0.24
2-hour glucose	109.5 (96–126)	122 (103–137) ^a	111 (97–125)	134 (103–158) ^{ab}	<0.0001
3 to 4 years prior to the end of the study					
	No Diabetes N = 156	Diabetes N = 43	No Diabetes N = 996	Diabetes N = 47	
Fasting glucose	89 (83–94)	87 (80–92)	86 (82–92)	87.5 (81–93)	0.15
2-hour glucose	111 (95–125.5)	115 (98–125)	108.5 (94–123.5)	116 (102–153)	0.11
4 to 5 years prior to the end of the study					
	No Diabetes N = 128	Diabetes N = 23	No Diabetes N = 71	Diabetes N = 19	
Fasting glucose	85 (81–90)	86 (76–92)	88 (83–92)	89 (86–95)	0.07
2-hour glucose	107 (95–119.5)	113 (93–127)	107 (92–124)	124 (102–157) ^{ab}	0.03

Data presented as median with IQ range

^a p<0.05, vs. oral study no diabetes^b p<0.05, vs. oral study diabetes^c p<0.05, vs. parenteral study no diabetes

TABLE 3

Cox Proportional Hazards Modeling for Time to Diabetes

ORAL TRIAL			
Parameter	Hazard Ratio	Chi-Square	p- value
BMI Z-score	1.381 (1.096–1.740)	7.49	0.0062
FPIR	0.992 (0.986–0.999)	5.20	0.023
2-hour glucose	1.016 (1.009–1.024)	18.26	<0.0001
HOMA-R	1.232 (0.983–15.46)	3.27	0.07
PARENTERAL TRIAL			
Parameter	Hazard Ratio	Chi-Square	p- value
BMI Z-score	1.316 (0.960–1.804)	2.92	0.09
FPIR	0.990 (0.983–0.997)	6.96	0.008
2-hour glucose	1.004 (1.001–1.008)	6.63	0.01
HOMA-R	1.258 (1.037–1.527)	5.41	0.02

Data presented are HR and 95% confidence interval.

Hazard for per $\mu\text{U/mL}$ increase in FPIR and per 1 mg/dL increase in 2-hour glucose

Table 4
Sensitivity and specificity of IVGTT and OGTT parameters by time to diabetes

Less than 6 months prior to diabetes or end of study		
	Sensitivity	Specificity
Fasting glucose ≥ 110 mg/dL	1.2% (7.3–1.9%)	97% (95–99%)
2 hr glucose ≥ 140 mg/dL	76% (67–83%)	78% (73–82%)
FPIR $< 10^{\text{th}}$ percentile	73% (60–83%)	66% (58–74%)
1 to 2 years prior to diabetes or end of study		
Fasting glucose ≥ 110 mg/dL	5% (2.7–8.8%)	99% (98–1.00%)
2 hr glucose ≥ 140 mg/dL	50% (43–57%)	86% (81–88%)
FPIR $< 10^{\text{th}}$ percentile	55% (47–63%)	73% (68–78%)
2 to 3 years prior to diabetes or end of the study		
Fasting glucose ≥ 110 mg/dL	1.5% (3.8–4.9%)	99% (97–1.00%)
2 hr glucose ≥ 140 mg/dL	31% (24–39%)	88% (84–91%)
FPIR $< 10^{\text{th}}$ percentile	44% (36–52%)	72% (66–77%)
> 5 years prior to diabetes or end of the study		
Fasting glucose ≥ 110 mg/dL	0% (0–1.7%)	1.00% (97–1.00%)
2 hr glucose ≥ 140 mg/dL	1.6% (5.5–38%)	96% (91–99%)
FPIR $< 10^{\text{th}}$ percentile	36% (22–52%)	70% (63–76%)

Data presented as sensitivity and specificity with 95% confidence intervals