Type 1 Diabetes Manifested Solely by 2-h Oral Glucose Tolerance Test Criteria

Carla J. Greenbaum, David Cuthbertson, Jeffrey P. Krischer, and the Diabetes Prevention Trial of Type 1 Diabetes Study Group

The clinical presentation of type 1 diabetes usually involves symptoms such as polyuria and polydipsia. However, investigators in the Diabetes Prevention Trial of Type 1 Diabetes (DPT-1) have detected a group of subjects with type 1 diabetes who have a different phenotype. These subjects are asymptomatic, have normal (<6.1 mmol/l) (group A) or impaired (6.1– <7.0 mmol/l) (group B) fasting glucose, but have 2-h glucose values >11.1 mmol/l on their oral glucose tolerance tests (OGTT). Of the 585 OGTTs performed on islet cell antibody (ICA)-positive relatives with insulin autoantibodies (IAA) or low first-phase insulin response (FPIR), normal glucose tolerance (NGT) was found in 427 subjects; impaired glucose tolerance (IGT) was found in 87 subjects, and diabetes was found by 2-h OGTT criteria alone in 61 subjects. Despite marked differences in 2-h glucose values (NGT 5.8 ± 1.1 mmol/l, IGT 8.9 ± 0.9 mmol/l, and group A 13.5 ± 2.5 mmol/l), there were no significant differences in fasting glucose values among NGT (4.8 ± 0.5 mmol/l), IGT (5.03 ± 0.5 mmol/l), and group A (4.99 ± 0.7 mmol/l) categories. Mean FPIR was higher in subjects with NGT compared with subjects with IGT and subjects diagnosed by 2-h OGTT criteria alone. However, the correlation between FPIR and 2-h glucose value was low (r^2 = 0.14). Multivariate analysis demonstrated that additional independent variables provide smaller contributions to the 2-h glucose value. In conclusion, there are asymptomatic type 1 diabetic subjects whose diabetes was diagnosed by the 2-h criteria on OGTT alone. Despite the importance of β-cell dysfunction in the pathogenesis of type 1 diabetes, factors other than impaired FPIR must also contribute to postprandial glucose tolerance in these subjects. *Diabetes* 50:470–476, 2001

From the Department of Veterans Affairs (C.J.G.), Puget Sound Health Care System and the Department of Medicine (C.J.G.), University of Washington, Seattle, Washington; and the H. Lee Moffitt Cancer Center and Research Institute (D.C., J.P.K.), University of South Florida, Tampa, Florida.

Address correspondence and reprint requests to Carla Greenbaum MD, Diabetes Clinical Research Unit, Clinical Research Center, Virginia Mason Research Center, 1201 9th Ave., Seattle, WA 98101. E-mail: cjgreen@vmresearch.org.

Received for publication 18 August 1999 and accepted in revised form 16 October 2000.

AUC, area under the curve; DPT-1, Diabetes Prevention Trial of Type 1 Diabetes; FPIR, first-phase insulin response; HOMA-β, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; IAA, insulin autoantibody; ICA, islet cell antibody; IDS, Immunology of Diabetes Society; IGT, impaired glucose tolerance; IVGTT, intravenous glucose tolerance test; JDF U, Juvenile Diabetes Foundation units; NDDG, National Diabetes Data Group; NGT, normal glucose tolerance; NIH, National Institutes of Health; OGTT, oral glucose tolerance test.

The clinical manifestation of type 1 diabetes usually involves symptoms such as polyuria and polydipsia and is thought to occur after autoimmune destruction of most of the pancreatic β-cells, resulting in severe insulin deficiency and fasting hyperglycemia. However, investigators in the Diabetes Prevention Trial of Type 1 Diabetes (DPT-1) (1,2) have detected a group of subjects with type 1 diabetes who have a different phenotype. These subjects are asymptomatic, have normal (<6.1 mmol/l) or impaired (6.1–<7.0 mmol/l) fasting glucose on their oral glucose tolerance tests (OGTTs), but have 2-h glucose values >11.1 mmol/l, thus meeting one of the American Diabetes Association's (3) new criteria for the diagnosis of diabetes. Importantly, these subjects have characteristics placing them at increased risk for type 1 diabetes; i.e., they are relatives of patients with type 1 diabetes, they are <45 years of age, and they are islet cell antibody (ICA)-positive.

The DPT-1 is a multicenter randomized trial designed to determine if type 1 diabetes can be prevented or delayed. First- or second-degree relatives of type 1 diabetic patients ≤45 years of age are screened for the presence of ICAs. Then, those who are ICA^+ enter the staging part of the DPT-1, during which they undergo tests to estimate their risk for developing diabetes more precisely. The last staging test performed before randomization into the treatment part of the study is an OGTT to rule out the presence of diabetes (1,2). Those with fasting or postprandial hyperglycemia on this OGTT are excluded from further participation. This report describes the population of subjects with type 1 diabetes identified by the 2-h OGTT criteria alone at the time of the DPT-1 staging OGTT. Demographic data (age, sex, and relationship to proband), immune activity (antibody status), and tests of β-cell function (first-phase insulin response [FPIR] and OGTT) are described for these subjects and compared with those subjects whose staging OGTT for DPT-1 classified them as having normal glucose tolerance (NGT) or impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS

Subjects. All of the subjects were participants in the DPT-1 who underwent an OGTT during the period from February 1994 through December 1998 (Fig. 1). Protocols were approved at participating locations nationwide, and all subjects (and/or parents of minors) gave written informed consent for each part of the study.

Screening. As of 31 December 1998, 65,758 first-degree (≤45 years of age) and second-degree (≤20 years of age) relatives of patients with type 1 diabetes were screened for the presence of ICAs. Those subjects whose ICA titer was ≥10 Juvenile Diabetes Foundation units (JDF U) were invited to participate in staging (n = 2,350).

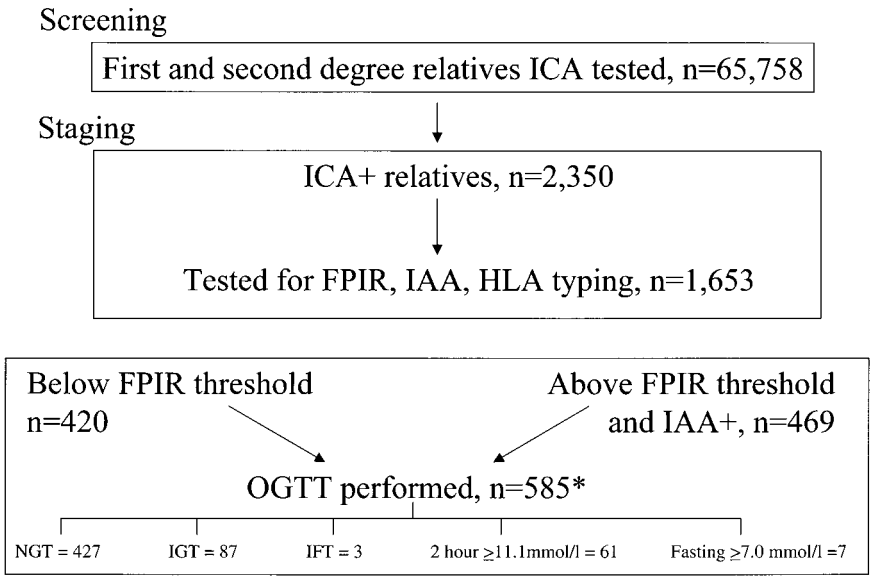

FIG. 1. DPT-1 screening and staging as of 31 December 1998. *OGTT results on eligible, consenting subjects whose results were available by December 1998. Exclusions were interim diagnosis of diabetes, presence of HLA DQB1*0602, medications or illness that may interfere with glucose metabolism or study compliance, and unable or unwilling to consent.

Staging. ICA+ relatives underwent intravenous glucose tolerance testing (IVGTT) to determine FPIR. In addition, repeat testing was performed for ICAs, and the presence of insulin autoantibodies (IAAs) was determined. Subjects with IVGTT insulin results below threshold (see below) on two occasions (n = 420) or who had ICAs as well as IAAs present (n = 469) were eligible for OGTT.
Autoantibody assays. ICA values were determined on frozen sections of human pancreas in the DPT-1 ICA core laboratory (Gainesville, FL, February 1994 to September 1997; and New Orleans, LA, September 1997 to December 1998). Values ≥10 JDF U were considered positive. In the 1995 Immunology of Diabetes Society (IDS) workshop, this ICA assay had a specificity of 100% with a sensitivity of 74.4% for recent onset patients <30 years of age.
Insulin autoantibody. IAA values were determined at the DPT-1 IAA core laboratory (Boston, MA) by a fluid-phase radioassay using 600 µl of sera with duplicate determinations with and without unlabeled insulin for competition. The interassay coefficient of variation for the IAA assay is 10.3% at low positive values. In the 1995 IDS workshop, this IAA assay had a specificity of 91% and a sensitivity of 49% for recent onset patients <30 years of age.
GAD65 and ICA512 antibodies. GAD65 and ICA512 antibodies (GAD65ab, ICA512ab) were determined in Denver, Colorado, on DPT-1 samples as part of an ancillary study. A combined GAD65ab and ICA512ab radioassay was performed (4). Labeled recombinant GAD65 and ICA512 were produced by in vitro transcription/translation with differential labeling (3H-GAD65 and 35S-ICA512). The levels of both antibodies were expressed as an index. The interassay coefficients of variation are 6 and 9.6% for GAD65ab and ICA512ab, respectively. The upper limits of normal (0.032 for GAD65ab; 0.071 for ICA512ab) were established as the 99th percentile for GAD65ab and as the 100th percentile for ICA512ab from receiver-operating characteristic curves in 198 healthy control subjects and 50 patients with recent- onset diabetes. In the 1995 IDS workshop, sensitivity for the GAD65ab assay was 82%, and specificity was 99%. Sensitivity for the ICA512ab assay was 73%, and specificity was 100%.
β-cell function. IVGTTs were performed according to the Islet Cell Antibody Register User's Study protocol (5,6). Fasting samples were drawn at –10 and –4 min through an intravenous line. A solution of 25% glucose (0.5 g/kg, maximum 35 g) was then given intravenously over 3 min. Samples were drawn at 1, 3, 5, 7, and 10 min after the end of the glucose infusion. Insulin and glucose were measured in the DPT-1 β-Cell Function core laboratory (Seattle, WA).

FPIR was calculated as the sum of the IVGTT insulin values at 1 and 3 min. The 10th percentile of normal control subjects for siblings and offspring >8 years of age is 600 pmol/l. The 10th percentile for siblings and offspring <8 years of age and the first percentile for parents is 360 pmol/l. FPIR below these values are defined as low and are used as the thresholds for eligibility for the parental insulin intervention trial.
Homeostasis model assessment of β-cell function. The homeostasis model assessment of β-cell function (HOMA-β) (7) was calculated as follows: fasting insulin (pmol)/[fasting glucose (mmol) – 3.5]
Homeostasis model assessment of insulin resistance. The homeostasis model assessment of insulin resistance (HOMA-IR) (7) was calculated as follows: [fasting insulin (pmol) × fasting glucose (mmol/l)]/22.5.
OGTT. After an overnight fast and insertion of an antecubital intravenous line, samples were drawn at –10 and 0 min. An oral glucose load was then administered (Fisherbrand Sun-dex) (1.75 g/kg, maximum 75 g). Blood samples were drawn at 30, 60, 90, and 120 min after glucose consumption. C-peptide and glucose were measured in the DPT-1 β-Cell Function core laboratory (Seattle, WA).
Statistical analysis. Variables that were not normally distributed (autoantibody titers, HOMA-β, HOMA-IR, C-peptide area under the curve (AUC), fasting insulin, FPIR, and fasting and 2-h glucose) were log-transformed for analysis. However, for clarity of interpretation, results are expressed as untransformed mean and SD values.

Differences in means of continuous variables were tested using analysis of variance. Tukey's studentized range test was used to control the experiment-wise error rate for pair-wise comparisons. Differences in categorical variables were tested using the χ^2 statistic and Fisher's exact test. Pair-wise comparisons were performed, altering the accepted level of statistical significance by a Bonferroni adjustment; with four groups, the acceptance level is 0.0083; with three groups, the acceptance level is 0.0167. Trends were assessed using Spearman's rho correlation analysis. Multivariate step-wise linear regression was performed using variables determined to be statistically significant by univariate analysis. Statistical significance for the regression analyses was accepted at 5%.

RESULTS

Glucose. As of 31 December 1998, there were 585 subjects who underwent a staging OGTT. NGT was found in 427 subjects, IGT was found in 87 subjects, and type 1 diabetes was diagnosed solely by the 2-h OGTT criteria in 61 subjects. The American Diabetes Association has also defined a category of impaired fasting glucose in which the fasting glucose value is between 6.1 and <7.0 mmol/l, and the 2-h value is <7.8 mmol/l. Because only three subjects had this glucose profile, they were not included in the analysis. However, the distinction between normal and impaired fasting glucose was applied to the subjects with diabetes diagnosed by their 2-h OGTT value, thus defining group A and group B categories (described below). There were an additional seven subjects excluded from the analysis who had fasting glucose ≥7.0 mmol/l and 2-h glucose ≥11.1 mmol/l (Table 1 and Fig. 2).

TABLE 1
Classification of ICA$^+$ and IAA/low FPIR relatives according to OGTT results

			OGTT ≥11.1 mol/l	
	NGT	IGT	Group A	Group B
n	427	87	36	25
Group criterion				
Fasting glucose (mmol/l)	<6.1	<6.1	<6.1	6.1–<7.0
2-h glucose (mmol/l)	<7.8	≥7.8, <11.1	≥11.1	≥11.1
Baseline characteristics				
Fasting glucose (mmol/l)	4.80 ± 0.46	5.03 ± 0.5	4.99 ± 0.67	6.47 ± 0.28*
2-h glucose (mmol/l)	5.82 ± 1.12*	8.93 ± 0.89*	13.54 ± 2.51*	15.19 ± 3.39*
Age (years)	12.6 ± 9.5 (2–44)	13.9 ± 11.0 (1–45)	11.8 ± 9.5 (2–40)	21.0 ± 14.1 (3–44)*
Sex				
Male	243 (56.9)	50 (57.5)	16 (44.4)	14 (56.0)
Female	184 (43.1)	37 (42.5)	20 (55.6)	11 (44.0)
Relationship to proband†				
Sibling	266 (62.3)	61 (71.1)	20 (55.6)	16 (64.0)
Offspring	113 (26.5)	19 (21.8)	10 (27.8)	4 (16.0)
Parent	15 (3.5)	3 (3.5)	2 (5.6)	5 (20.0)
Second-degree relative	33 (7.7)	4 (4.6)	4 (11.1)	0 (0.0)
Race/ethnicity				
Caucasian	381 (89.2)	80 (92)	34 (94.4)	22 (88.0)
African-American	6 (1.4)	3 (3.5)	0 (0.0)	0 (0.0)
Hispanic	22 (5.2)	2 (2.3)	2 (5.6)	1 (4.0)
Other	11 (2.6)	0 (0.0)	0 (0.0)	2 (8.0)
Unknown	7 (1.6)	2 (2.3)	0 (0.0)	0 (0.0)
Type 1 diabetes haplotypes‡	288 (66.8)	62 (71.3)	27 (75)	19 (73.1)
ICA titer (JDF U; median)	80 (10–40,960)	160 (10–2,560)	160 (10–5,120)	320 (20–2,560)
IAA$^+$	303 (71.0)	66 (75.9)	28 (77.8)	13 (52)
GAD65ab$^+$	184 (75.7)	33 (76.7)	14 (66.7)	9 (75.0)
ICA512ab$^+$†	113 (40.5)	30 (62.5)	11 (50.0)	7 (58.3)
Fasting insulin (pmol/l)	77.4 ± 51.6	72.2 ± 57.0	73.8 ± 32.4	117.6 ± 75.0*
HOMA-β§	59.4 ± 70.1	56.1 ± 37.0	50.9 ± 32.2	42.9 ± 24.2
HOMA-IR§	17.7 ± 17.8	19.2 ± 14.4	16.5 ± 8.5	32.8 ± 22.7*
FPIR (pmol/l)§	724 ± 485*	462 ± 388	365 ± 215	279 ± 154

Data are means ± SD, means ± SD (range), and *n* (%). *Significantly different from other group by analysis of variance (*F* test and Duncan's range test); †statistically significant by χ^2 analysis; ‡DQA1*0501/DQB1*0201 and DQA1*0301/DQB1*0302; §statistically significant trend by Spearman's rho.

Groups were defined according to 2-h glucose value. Therefore, as expected, the mean values were different among those with NGT (5.8 ± 1.1 mmol/l), those with IGT (8.9 ± 0.9 mmol/l), and those with diabetes diagnosed by the 2-h glucose criteria (14.2 ± 3.0 mmol/l) ($P < 0.001$). When the latter group was divided between subjects with normal fasting glucose (group A) and subjects with impaired fasting glucose (group B), there was also a difference in 2-h glucose values (group A 13.5 ± 0.4 mmol/l and group B 15.2 ± 3.4 mmol/l; $P < 0.001$). Despite these marked differences in 2-h glucose values, the difference in fasting glucose values among NGT (4.8 ± 0.5 mmol/l), IGT (5.02 ± 0.5 mmol/l), and group A (4.99 ± 0.7 mmol/l) diabetes groups was not significant.

Demographic data. Univariate analysis demonstrated no differences with respect to age, ethnic affiliation, relationship of subject to proband with diabetes, or sex among groups defined as NGT, IGT, or diabetes by 2-h criteria only. However, those in group B were older ($P < 0.001$), more likely to be a parent of the proband with diabetes, and less likely to be a second-degree relative of the diabetic proband ($P = 0.012$) than those with NGT (Table 1). Height and weight data was not collected on subjects in the staging part of DPT-1 until early 1999; therefore, this data is not available for the population described in this study. However, analysis of data obtained on subjects undergoing OGTT since that date indicates no significant difference in either trend or average among groups with respect to BMI, although the number is small.

Genetic data. The haplotypes DQA1*0501/DQB1*0201 and DQA1*0301/DQB1*0302 are commonly associated with type 1 diabetes. There were no differences in the frequency of these haplotypes between glucose tolerance groups (Table 1).

Antibody data. IAA and ICA data were available on all 585 subjects, as they were obtained as part of DPT-1 protocol. GAD65ab and ICA512ab were obtained as part of a DPT-1 ancillary study; therefore, results were available for only 323 of these samples. For both IAA and GAD65 antibodies, there were no differences in the percent positive (Table 1) or in titers (data not shown) between OGTT groups. Similarly, the median ICA titers were the same between groups. There was also no significant trend relating any of these antibodies with worsening glucose tolerance. Though the percent of subjects that were ICA512ab$^+$ in each group was statistically different by χ^2 analysis ($P = 0.017$), there was no significant trend with worsening glucose tolerance, and the median titers were not different by OGTT group (data not shown).

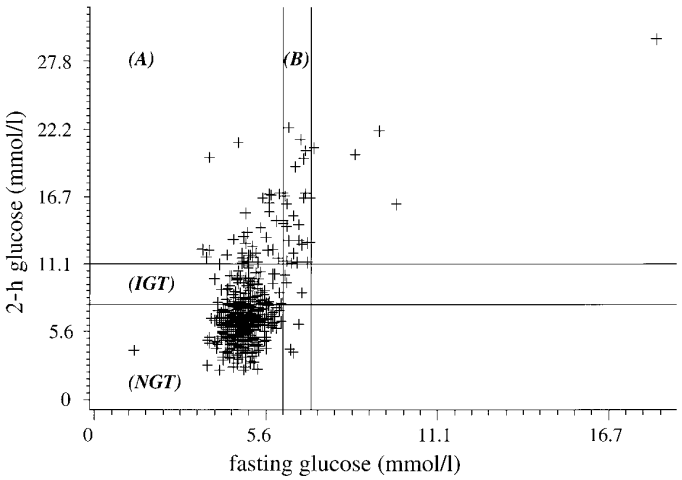

FIG. 2. Relationship between fasting and 2-h glucose value from OGTT in 585 ICA$^+$ relatives with IAA and/or low FPIR. *A*, group A; *B*, group B.

Metabolic data

Basal insulin secretion. Fasting insulin values were not different among subjects with NGT (77.4 ± 51.6 pmol/l), IGT (82.2 ± 57 pmol/l), and diabetes diagnosed by 2-h criteria alone (90.8 ± 56.8 pmol/l), although there was a difference between group A (73.8 ± 32.4 pmol/l) and group B (117.6 ± 75 pmol/l). Similarly, though the HOMA-β indexes were the same by OGTT group (NGT 59.4 ± 70.1, IGT 56.1 ± 37.0, and diabetes by 2-h OGTT criteria 49.2 ± 29.4), there was a weak but statistically significant correlation among each of these variables and categories of worsening glucose tolerance (fasting insulin $r = 0.09$, $P = 0.04$; and HOMA-β $r = -0.09$, $P = 0.03$).

There were no differences in the HOMA-IR index among NGT (17.7 ± 17.8), IGT (19.2 ± 14.4), and group A (16.5 ± 8.5) categories. However, the HOMA-IR index in group B was significantly increased (32.8 ± 22.7), and there was a weak but statistically significant trend between the HOMA-IR values and the categories of worsening glucose tolerance ($r = 0.13$, $P = 0.001$).

Stimulated insulin secretion. Fewer of the relatives with NGT had low FPIR compared with the other OGTT groups ($P < 0.001$). This was also reflected in the mean values for each group, with a significantly higher FPIR in those with NGT (724 ± 485 pmol/l) than in those with IGT (462 ± 338 pmol/l), group A (365 ± 215 pmol/l) or group B (279 ± 154 pmol/l) ($P <$ 0.001). There were no significant differences among the latter three groups as categories; however, there was a significant trend of decreasing FPIR with worsening glucose intolerance (Fig. 3) ($r = -0.27$, $P < 0.001$). Comparing only those subjects in each glucose tolerance group who had a low FPIR ($n = 304$; 52% of subjects), there was a difference in mean FPIR between those with NGT (392.3 ± 127.9 pmol/l) and IGT (310.7 ± 108.8 pmol/l), group A (289.0 ± 140.5 pmol/l), and group B (266.5 ± 135.5 pmol/l) ($P < 0.001$).

To explore the relationship between FPIR and glucose values further, we compared FPIR with fasting glucose or 2-h glucose as continuous variables. Though there was a statistically significant relationship between FPIR and each glucose measure, the correlation of these measures was weak (Figs. 4 and 5). A similar relationship was found when only those with low FPIR were examined (data not shown). Similar results were obtained using C-peptide measurements during the OGTT as a measure of insulin secretion; i.e., there was a statistically significant relationship ($P = 0.0001$) between the 2-h glucose value and the C-peptide AUC or the increment from 0–30 min. However, the correlations were low ($R^2 = 0.03$ for AUC and 0.11 for the 0–30 min increment).

We then analyzed the correlations between variables (Table 2) and performed multivariate stepwise linear regression analysis to determine the independent contribution of variables of interest in explaining the 2-h glucose values. Because of the close correlation ($R = 0.84$) between glucose AUC and 2-h glucose value, glucose AUC was not considered an independent variable. The independent variables tested

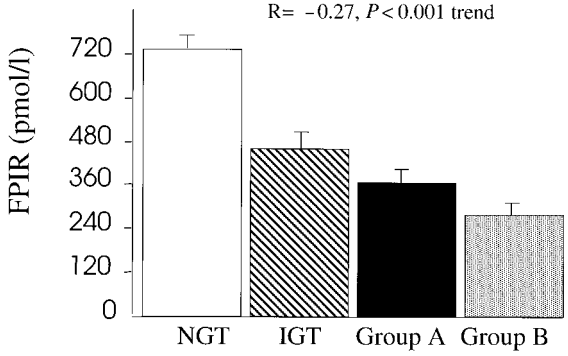

FIG. 3. Means ± SE FPIR according to OGTT group.

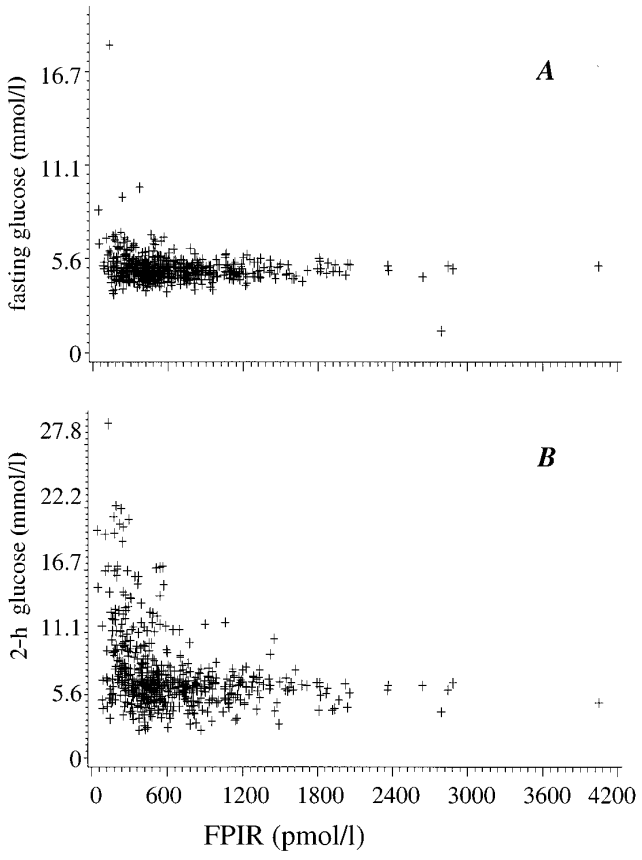

FIG. 4. *A*: FPIR vs. fasting glucose from OGTT; $R^2 = 0.06$. *B*: FPIR vs. 2-h glucose from OGTT; $R^2 = 0.14$.

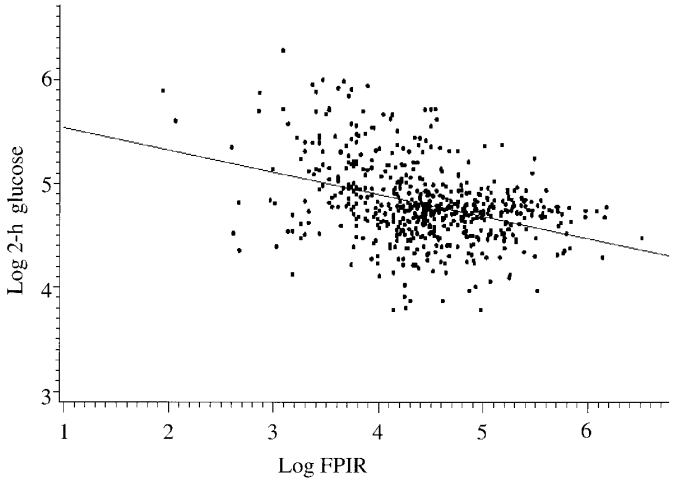

FIG. 5. Log-transformed FPIR vs. 2-h glucose from OGTT; R^2 = 0.14.

include FPIR, fasting insulin, fasting glucose, HOMA-IR, HOMA-β, IAA titer, relationship to proband, ethnicity, incremental C-peptide between 0–30 min, and C-peptide AUC. In addition to FPIR, the variables that significantly, though weakly, contributed to 2-h glucose were fasting glucose, IAA titer, HOMA-IR, and OGTT C-peptide values (both incremental C-peptide between 0 and 30 min and C-peptide AUC). Together, these independent variables were only moderately correlated with 2-h glucose (model R^2 = 0.39).

DISCUSSION

This study describes a previously unrecognized group of subjects with asymptomatic type 1 diabetes. These subjects have normal or impaired fasting glucose values and elevated 2-h glucose values on OGTT. The validity of our observation is indicated by the fact that there is no absolute difference or trend of higher values in fasting glucose among those with NGT, IGT, and diabetes diagnosed by 2-h glucose alone, despite moderate (IGT) or marked (diabetic) 2-h hyperglycemia. In addition, repeat OGTT was performed on 14 subjects with diabetes diagnosed by 2-h OGTT criteria alone, and either IGT or diabetes with normal fasting glucose was confirmed in 13 of the subjects. Importantly, these subjects have characteristics associated with type 1 diabetes; they are relatives of subjects with type 1 diabetes, they are between 3 and 45 years of age, they are ICA^+, and 53% have markedly abnormal first-phase insulin release.

Type 1 diabetes is believed to occur because of an autoimmune-mediated process resulting in progressive β-cell destruction. Loss of first-phase insulin release occurs before the onset of clinical disease, and it is the most powerful predictor for the development of overt hyperglycemia and associated symptoms. Our data indicate a statistically significant but weak correlation of FPIR with categories of worsening glucose tolerance. This supports the concept that subjects with diabetes diagnosed solely by their 2-h OGTT glucose value represent a previously undescribed intermediate step on the path from NGT to overt diabetes. Interestingly, postprandial hyperglycemia seen in relatives of type 2 diabetic subjects before overt diabetes was also associated with alterations in β-cell function (8), even though those subjects also had slight elevations in fasting glucose as compared with the type 1 diabetic subjects described in this study.

However, the relationship between FPIR and glucose status is not entirely straightforward, as we were unable to find a robust direct relationship between FPIR and 2-h glucose value. At the extremes of the curves, subjects with the highest glucose values had low FPIR, and subjects with high FPIR had lower glucose values. However, among subjects with a low FPIR (600 pmol/l), 2-h glucose values ranged between 2.8 and 30.5 mmol/l. This suggests that low FPIR is necessary, but not sufficient for postprandial hyperglycemia. Though statistically significant, the low R^2 value of 0.14 suggests that 86% of the variance is due to factors other than FPIR.

If not fully accounted for by FPIR, then what additionally accounts for the state of glucose intolerance in these subjects? Although stepwise linear regression analysis identified other factors, the ability of all variables to predict 2-h glucose was only moderate (R^2 = 0.39), suggesting that 61% of variance in 2-h glucose remains unexplained based on these data. There are several possibilities. Because the β-cell's response to glucose is only one measure of β-cell function, further β-cell destruction manifested by a lack of insulin release to nonglucose secretagogues may be required before postprandial hyperglycemia is seen. In this scenario, it may be that the β-cell's inability to respond to the incretin hormones (GLP-1, GIP) would result in postprandial hyperglycemia.

Alternatively, though the primary defect in these subjects is impairment in insulin secretion, it is possible that variations in insulin or glucose action could contribute to the 2-h hyperglycemia. The older age, increased fasting insulin, and increased HOMA-IR values among the subjects in group B suggests that the mild elevation in fasting hyperglycemia may be due to a relatively greater degree of insulin resistance com-

TABLE 2
Correlations (r values on log-transformed variables)

	Fasting glucose	HOMA-β	C-peptide AUC	C-peptide change 0–30 min	FPIR	2-h glucose	Glucose AUC	HOMA-IR
Fasting insulin	0.16	0.59	0.43	0.19	0.45	0.12	0.11	0.96
Fasting glucose	—	–0.26	0.06	–0.20	–0.24	0.46	0.54	0.25
HOMA-β	—	—	0.28	0.24	0.41	–0.10	–0.15	0.38
C-peptide AUC	—	—	—	0.73	0.54	–0.18	–0.13	0.39
C-peptide change 0–30 min	—	—	—	—	0.57	–0.42	–0.37	0.15
FPIR	—	—	—	—	—	–0.38	–0.45	0.40
2-h Glucose	—	—	—	—	—	—	0.84	0.17
Glucose AUC	—	—	—	—	—	—	—	0.17

pared with the younger subjects. Because the difference between group A and group B is primarily the fasting glucose values, the HOMA-IR data support the concept that failing β-cell secretion is reflected in an inability to handle an oral glucose load, but that fasting hyperglycemia in this population occurs only with the additional burden of insulin resistance. Though we do not have information about the presence of type 2 diabetes in the families of these subjects, the genotyping data suggest that these subjects are not genetically unusual type 1 diabetic patients, and implies that insulin resistance may contribute to the manifestation of type 1 diabetes in some people. In this regard, they share characteristics with the group of antibody-positive adults clinically presenting with type 2 diabetes (latent autoimmune disease in adults) (9–11), who may also represent part of the continuum of the autoimmune diabetes disease process modified by insulin resistance and other unknown factors.

The observation that some relatives of type 1 diabetic patients have abnormal glucose responses to OGTT is not new. Almost 30 years ago Burkeholder et al. (12) described significant nonfasting OGTT abnormalities in 25 children after testing 138 asymptomatic siblings of type 1 diabetic patients, of whom only 2 subsequently developed overt diabetes. Fajans et al. (13,14) mentioned that some patients manifest diabetes only by their postprandial glucose value. Several authors noted that abnormalities in postprandial glucose tolerance (chemical diabetes) were often associated with normal or elevated insulin values. In these subjects, reversion to NGT was frequent (15–18). Thus, the clinical significance of postprandial glucose elevation or episodes of transient hyperglycemia was unclear.

In 1978, the National Diabetes Data Group (NDDG) set criteria for the diagnosis of diabetes. Adults under that classification were defined as having diabetes when there was a 2-h and one other value on an OGTT that was ≥11.1 mmol/l in the presence of normal fasting glucose. In contrast, for children, abnormal postprandial glucose values alone were not sufficient to classify a child as having diabetes; instead, these children were defined as having IGT. Thus, the children with diabetes described in this report would not have been diagnosed with diabetes according to the previous criteria. The reason for developing more precise criteria for the diagnosis of diabetes in children relates to the lack of either retrospective or prospective data indicating the "significance of IGT in children and its relationship to the development of frank disease and diabetic complications" (19).

Recently established American Diabetes Association criteria for the diagnosis of diabetes require having one of the following on two occasions: *1*) symptoms of diabetes and plasma glucose ≥11.1 mmol/l, *2*) fasting glucose ≥7.0 mmol/l, or *3*) 2-h plasma glucose ≥11.1 mmol/l during an OGTT. Subjects with fasting glucose values of 6.1–6.9 mmol/l would be classified as having impaired fasting glucose and those with 2-h values of 7.8–11 mmol/l as having IGT. It is important to note that similar to the data used for the 1978 NDDG criteria (19), these values are based on data from the Pima Indian Study (20), the National Health and Nutrition Examination Survey III, the Paris Prospective Study (21), and an Egyptian study (22) (all adult populations who are at risk for type 2 diabetes). These committees did not consider the significance of postprandial hyperglycemia alone in children because there was no clear evidence that this population of subjects existed. In this context, it is important to note that subjects in our study with diabetes diagnosed by 2-h glucose criteria are no different from subjects with NGT with respect to age. Additionally, though we do not have BMI data on the subjects described in this study, analysis of a smaller number of subjects studied since 1999 suggests no differences between OGTT groups. Thus, having postprandial hyperglycemia and normal fasting glucose is not a finding related to age or weight, but rather is seen in people at risk for type 1 diabetes, even into adulthood.

There are several implications to the identification of this subset of subjects with type 1 diabetes. First, it is not clear what the natural history of these subjects will be over time. All of these subjects were identified through the DPT-1 as being in the population of subjects at a 25% or greater risk of developing clinical type 1 diabetes over a 5-year period; thus, we are not suggesting that postprandial hyperglycemia is commonly present in normal healthy subjects without islet cell autoimmunity. In addition, a prospective study of relatives with IGT defined by NDDG criteria demonstrated a threefold greater risk for subsequent type 1 diabetes than relatives with a normal OGTT (23). Nonetheless, whether these subjects will rapidly progress to overt symptomatic diabetes with fasting hyperglycemia, remain with postprandial hyperglycemia, or revert to normal glucose tolerance is unknown. A prospective study to answer these questions is underway and will assist clinicians in making therapeutic decisions. Second, until results from the ongoing DPT-1 and other intervention studies are available, we will not know whether early intervention is beneficial for preventing the progression of disease. Third, as expressed by the NDDG team in 1978, we still do not know whether early diagnosis is beneficial regarding prevention of long-term complications of diabetes. Therefore, because our data show that some asymptomatic type 1 diabetic subjects develop postprandial hyperglycemia in the presence of normal fasting glucose, we suggest that treatment in nonpregnant subjects is not necessary at this stage. Frequent re-evaluation and counseling for the potential future progression of their disease should be recommended.

Importantly, the identification of this group of subjects also allows for further investigation as to the mechanisms contributing to postprandial hyperglycemia while normal fasting glucose is maintained. If abnormalities in other components of glucose homeostasis, i.e., insulin sensitivity, glucose disposal, or incretin response, are found to contribute to type 1 diabetes, it would suggest heterogeneity in this disease analogous to type 2 diabetes, with implications for genetic investigations and development of pharmacological treatments, in addition to insulin therapy.

ACKNOWLEDGMENTS

DPT-1 is supported through cooperative agreements by the Division of Diabetes, Endocrinology and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health (NIH); the National Institute of Allergy and Infectious Disease, NIH; the National Institute of Child Health and Human Development, NIH; the National Center for Research Resources, NIH; the American Diabetes Association; the Juvenile Diabetes Foundation International; and various corporate sponsors.

Additional support was obtained from an American Diabetes Association Clinical Research Award and a Research

Associate Career Development Award from the Department of Veterans Affairs. These investigations also relied on the Clinical Research Centers at DPT-1 sites, including the University of Washington (N01RR00037).

The authors would also like to thank Ronald Prigeon, MD, for his helpful discussion of the data and George Eisenbarth, MD, for use of ICA512ab and GAD65ab data.

REFERENCES

1. DPT-1 Study Group: The Diabetes Prevention Trial of Type 1 Diabetes (Abstract). *Diabetes* 43 (Suppl. 1) 159A, 1994
2. DPT-1 Study Group: The Diabetes Prevention Trial of Type 1 Diabetes: implementation of screening and staging of relatives (Abstract). *Diabetes* 44 (Suppl. 1):129A, 1995.
3. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 20:1183–1197, 1997
4. Yu L, Rewers M, Gianani R, Kawasaki E, Zhang Y, Verge C, Chase P, Klingensmith G, Erlich H, Norris J, Eisenbarth GS: Antiislet autoantibodies usually develop sequentially rather than simultaneously. *J Clin Endocrinol Metab* 81:4264–4267, 1996
5. Bingley PJ, ICARUS Group: Interactions of age, islet cell antibodies, insulin autoantibodies, and first-phase insulin response in predicting risk of progression to IDDM in ICA$^+$ relatives: the ICARUS data set. *Diabetes* 45:1720–1728, 1996
6. McCulloch D, Bingley P, Colman P, Jackson R, Gale E, ICARUS Group: Comparison of bolus and infusion protocols for determining acute insulin response to intravenous glucose in normal humans. *Diabetes Care* 16:911–915, 1993
7. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
8. Byrne M, Sturis J, Sobel R, Polonsky K: Elevated plasma glucose 2 h postchallenge predicts defects in β-cell function. *Am J Physiol* 33:E572–E579, 1996
9. Carlsson A, Sundkvist G, Groop L, Tuomi T: Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA). *J Clin Endocrinol Metab* 85:76–80, 2000
10. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissén M, Ehrnström BO, Forsén B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC: Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. *Diabetes* 48:150–157, 1999
11. Zimmet PZ, Elliott RB, Mackay IR, Tuomi T, Rowley MJ, Pilcher CC, Knowles WJ: Autoantibodies to glutamic acid decarboxylase and insulin in islet cell antibody positive presymptomatic type 1 diabetes mellitus: frequency and segregation by age and gender. *Diabet Med* 11:866–871, 1994
12. Burkeholder JN, Pickens JM, Womack WN: Oral glucose tolerance test in siblings of children with diabetes mellitus. *Diabetes* 16:156–160, 1967
13. Fajans SS, Cloutier MC, Crowther RL: Banting lecture: clinical and etiological heterogeneity of idiopathic diabetes mellitus. *Diabetes* 27:1112–1125, 1978
14. Fajans SS: Heterogeneity within type II and MODY diabetes. In *Comparison of Type 1 and Type II Diabetes: Advances in Experimental Medicine and Biology*. Vranic M, Hollenberg CH, Steiner G, Eds. New York, Plenum Publishing, 1985, p. 65–87
15. Reaven GM, Olefsky JM: Relationship between heterogeneity of insulin responses and insulin resistance in normal subjects and patients with chemical diabetes. *Diabetologia* 13:201–206, 1977
16. Rosenbloom AL: Insulin responses of children with chemical diabetes mellitus. *N Engl J Med* 282:1228–1232, 1970
17. Rosenbloom AL, Wheeler L, Bianchi R, Chin FT, Tiwary CM, Grgic A: Age-adjusted analysis of insulin responses during normal and abnormal glucose tolerance tests in children and adolescents. *Diabetes* 24:820–828, 1975
18. Rosenbloom AL, Hunt SS, Rosenbloom EK, Maclaren NK: Ten-year prognosis of impaired glucose tolerance in siblings of patients with insulin-dependent diabetes. *Diabetes* 31:385–387, 1982
19. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
20. McCance DR, Hanson RL, Charles MA, Jacobsson LTH, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests of glycated hemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308:1323–1328, 1994
21. Charles MA, Balkau B, Vauzelle-Kervoeden F, Thibult N, Eschwege E: Revision of diagnostic criteria for diabetes. *Lancet* 348:1657–1658, 1996
22. Engelgau MM, Thompson TJ, Herman WH, Boyle JP, Aubert RE, Kenny SJ, Badran A, Sous ES, Ali MA: Comparison of fasting and 2-h glucose and HbA_{1c} levels for diagnosing diabetes: diagnostic criteria and performance revisited. *Diabetes Care* 20:785–791, 1997
23. Lipton RB, Atchison J, Dorman JS, Duquesnoy RJ, Eckenrode K, Orchard TJ, LaPorte RE, Riley WJ, Kuller LH, Drash AL, Becker DJ: Genetic, immunological, and metabolic determinants of risk for type 1 diabetes mellitus in families. *Diabet Med* 9:224–232, 1992