Impaired β-Cell Function, Incretin Effect, and Glucagon Suppression in Patients With Type 1 Diabetes Who Have Normal Fasting Glucose

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We have recently described a novel phenotype in a group of subjects with type 1 diabetes that is manifested by glucose >11.1 mmol/l 120 min after an oral glucose load, but with normal fasting glucose levels. We now describe the metabolic characteristics of these subjects by comparing parameters of islet hormone secretion and glucose disposal in these subjects to age-matched nondiabetic control subjects. The patients with type 1 diabetes had fasting glucose, insulin, and glucagon values similar to those of control subjects. Additionally, the insulin secretory response to intravenous arginine at euglycemia was similar in the control and diabetic groups (264 ± 33.5 and 193 ± 61.3 pmol/l; $P = 0.3$). However, marked differences in β-cell function were found in response to hyperglycemia. Specifically, the first-phase insulin response was lower in diabetic subjects (329.1 ± 39.6 vs. 91.3 ± 34.1 pmol/l; $P < 0.001$), as was the slope of glucose potentiation of the insulin response to arginine (102 ± 18.7 vs. 30.2 ± 6.1 pmol/l per mmol/l; $P = 0.005$) and the maximum insulin response to arginine (2,524 ± 413 vs. 629 ± 159 pmol/l; $P = 0.001$). Although plasma levels of glucagon-like peptide (GLP)-1 and gastric inhibitory peptide (GIP) did not differ between control and diabetic subjects, the incretin effect was lower in the diabetic patients (70.3 ± 5.4 vs. 52.1 ± 5.9%; $P = 0.03$). Finally, there was a lack of suppression of glucagon in the patients after both oral and intravenous glucose administration, which may have contributed to their postprandial hyperglycemia. Glucose effectiveness did not differ between patients and control subjects, nor did insulin sensitivity, although there was a tendency for the patients to be insulin resistant (9.18 ± 1.59 vs. 5.22 ± 1.17 pmol · l^{-1} · min^{-1}; $P = 0.08$). These data characterize a novel group of subjects with type 1 diabetes manifested solely by hyperglycemia following an oral glucose load in whom islet function is normal at euglycemia, but who have marked defects in both α- and β-cell secretion at hyperglycemia. This pattern of abnormalities may be characteristic of islet dysfunction early in the development of type 1 diabetes. *Diabetes* 51:951–957, 2002

An unchecked autoimmune process is thought to result in the progressive loss of β-cell function and the development of type 1 diabetes. Clinically, the disease often presents abruptly with severe, symptomatic hyperglycemia with or without ketoacidosis. Despite the apparent acute onset, it is currently thought that the destruction of islet β-cells occurs over a course of months to years, with affected subjects having variable periods of subclinical disease (1–6). Such people can be identified before the onset of clinically apparent diabetes by the presence of islet autoantibodies and reduction of first-phase insulin secretion. We have recently described a group of subjects with type 1 diabetes who have a distinct profile of abnormal glucose regulation. In these individuals, fasting glucose levels are normal (<6.1 mmol/l), but severe hyperglycemia occurs following an oral glucose load (glucose >11.1 mmol/l 120 min after glucose ingestion) (7). These subjects are first- and second-degree relatives of individuals with type 1 diabetes that was discovered during screening for the Diabetes Prevention Trial, type 1 (DPT-1). They have antibodies to islet cell antigens and were excluded from the DPT-1 because of their oral glucose tolerance test (OGTT) results.

Individuals with the unique metabolic profile of normal fasting glucose but diabetic oral glucose tolerance comprised only a minority of the subjects evaluated for the DPT-1 (~10%). However, we have noted that many of these individuals retain this distinct metabolic profile over periods of months to years (8). Thus, these individuals are at an intermediate stage between a preclinical high-risk state and typical type 1 diabetes with elevated fasting and postprandial glucose levels. As such, they represent an opportunity for physiologic characterization of a novel stage of autoimmune diabetes. Therefore, we sought to determine the processes regulating glucose metabolism that permit these subjects to maintain fasting euglycemia while being unable to regulate glycemia following a glucose challenge. Specifically, we assessed β-cell secretion in response to glucose and arginine, the regulation of glucagon release, the incretin effect (the insulinotropic actions of gastrointestinal hormones and neural stimuli to augment the β-cell response beyond glycemic stimulation

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ADA, American Diabetes Association; AIR, acute insulin response; AUC, area under the curve; DPT-1, Diabetes Prevention Trial, type 1; FPIR, first-phase insulin release; GIP, gastric inhibitory peptide; GLP, glucagon-like peptide; ICA, islet cell antibody; IVGTT, intravenous glucose tolerance test; MODY, maturity-onset diabetes of the young; NIH, National Institutes of Health; OGTT, oral glucose tolerance test; RIA, radioimmunoassay; S_G, glucose effectiveness index; S_I, insulin sensitivity index.

alone), insulin sensitivity, and glucose effectiveness. The results of these studies demonstrate a spectrum of abnormalities in islet hormone secretion that contribute to the dissociation of fasting and postprandial glucose control among individuals with early type 1 diabetes.

RESEARCH DESIGN AND METHODS

Subjects. Study subjects were identified during recruitment for DPT-1, a multicenter randomized trial to determine whether type 1 diabetes can be prevented or delayed. First- or second-degree relatives of patients with type 1 diabetes up to 45 years of age were screened for the presence of islet cell antibodies (ICAs). Those who were ICA-positive then had measurement of insulin autoantibodies and first-phase insulin release (FPIR) in response to intravenous glucose to more precisely estimate their risk for diabetes development. Those ICA-positive individuals with insulin autoantibodies or diminished FPIR (defined as the sum of insulin values 1 and 3 min after an intravenous glucose bolus: <600 pmol/l for siblings and offspring ≥8 years of age [their 10th percentile]; <360 pmol/l for siblings and offspring <8 years of age [their 10th percentile]; or <360 pmol/l for parents [their 1st percentile]) underwent OGTT to determine glucose tolerance status. Subjects with a fasting glucose ≥6.1 mmol/l, or a 120-min value >11.1 mmol/l during staging or while on study, were excluded from further participation in DPT-1. The protocol was approved by the Human Subjects Review Committee of the University of Washington, and informed consent was obtained from all subjects. Three groups of subjects were selected for the studies described herein.

Type 1 diabetic subjects. Type 1 diabetic subjects were ICA-positive individuals with normal fasting glucose values (<6.1 mmol/l) excluded from DPT-1 because of abnormal glycemia (>11.1 mmol/l) following an oral glucose load. We have termed this group "type 1 diabetes" even though they differ from typical type 1 diabetic patients in whom both fasting and postload glucose values are abnormal. The 17 subjects with diabetes in these studies had a mean age of 23.5 ± 14.4 years (mean ± SD), BMI 17.1 ± 6.5 kg/m^2, and mean HbA_{1c} 5.9 ± 0.4%.

DPT-1 control subjects (DPT). DPT subjects were ICA-positive individuals who were enrolled in the DPT-1. These subjects had diminished FPIR but did not have a diabetic OGTT result. The eight DPT subjects participating in this study had a mean age of 26.2 ± 13.1 years. Due to restrictions on active participants of the DPT-1, only limited studies on subjects enrolled in this group were possible.

Healthy control subjects. The 14 control subjects had no personal or family history of diabetes. They had a mean age of 26.8 ± 3.0 years, BMI 20.2 ± 2.6 kg/m^2, and mean HbA_{1c} 5.38 ± 0.3%.

Procedures. After an overnight fast, subjects reported to the Clinical Research Center and had intravenous catheters placed in one or both forearms. On separate days, they underwent one or more of the following procedures.

Oral glucose tolerance test. After fasting blood samples were drawn, subjects ingested an oral glucose solution (1.75 g/kg, maximum 75 g) within 5 min. Blood samples were drawn at 30, 60, 90, and 120 min after the start of glucose consumption.

Insulin modified frequently sampled intravenous glucose tolerance test (9). After three basal blood samples were taken, an intravenous bolus of 300 mg/kg glucose as a 50% solution was infused over 30 s, and blood samples were drawn at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 19 min after the start of the glucose bolus. At 20 min, insulin (0.02 U/kg for type 1 diabetic and DPT subjects, 0.03 units/kg for control subjects) was administered intravenously over 5 min. Further blood sampling was done at 22, 24, 27, 30, 32, 34, 35, 37, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min.

Incretin effect (10). After fasting blood samples were taken, an infusion of 20% dextrose was started. Blood glucose concentration was measured at 5-min intervals using bedside glucose reflectance strips (Glucometer; Bayer, Tarrytown, NY), and the dextrose infusion was varied to match the glucose concentrations during the OGTT. Blood samples for insulin measurement were obtained at 30, 60, 90, and 120 min.

Assessment of insulin/glucose slope and glucose potentiation of insulin secretion (11–13). After basal blood samples were taken (−10, 0 min), arginine (5 g) was given as an intravenous bolus, and blood samples were taken at 2, 3, 5, 7, and 10 min. Subsequently, a 20% glucose solution was infused to raise the blood glucose level to ~11–14 mmol/l over 20 min. Baseline blood samples were taken at this level of hyperglycemia (–5 and –1 min), 5 g arginine was infused, and blood sampling was repeated 2, 3, 5, 7, and 10 min later. Glucose was then infused to raise and maintain blood glucose at a level of >22.2 mmol/l over 20 min, and a third arginine bolus and blood sampling were repeated.

Biochemical determinations. Glucose was measured in plasma using a hexokinase method. Insulin (14), C-peptide, gastric inhibitory peptide (GIP) (15), and glucagon-like peptide (GLP)-1 (16) concentrations were measured using previously reported radioimmunoassays (RIAs). Glucagon was assayed using a commercially available RIA (Linco Research, St. Charles, MO).

Calculations. Indexes of insulin sensitivity (S_I) and glucose effectiveness (S_G) were calculated from glucose and insulin values during the intravenous glucose tolerance test (IVGTT) using the minimal model of glucose kinetics (17). The acute insulin response to glucose (AIR_g) was computed from the insulin values during the IVGTT as the mean of the incremental insulin concentrations above basal levels obtained during the first 10 min. The acute insulin response to arginine (AIR_{arg}) was quantified as the mean incremental insulin above baseline levels in the first 5 min following arginine injection. The insulin and glycemic responses during the OGTT and incretin studies were calculated as the area under the curve (AUC) above basal using the trapezoidal rule.

Two other measures of the effect of glucose on β-cell function were computed. The first examined the slope of the regression line of insulin concentration versus prevailing glucose concentration (insulin/glucose slope) using two points (fasting glucose and glucose ~11–14 mmol/l). The insulin values used for this computation were the average of the two baseline samples just before the arginine injection. The second slope was a measure of glucose potentiation of the insulin response to arginine (13). This parameter was computed in the same manner as the insulin/glucose slope, except that AIR_{arg} was used instead of the baseline insulin concentrations.

The incretin effect was calculated for each individual from the insulin responses during the OGTT and matched intravenous glucose infusion using the following formula (10):

$$100 \times (\text{insulin AUC}_{\text{OGTT}} - \text{insulin AUC}_{\text{IV glucose}})/\text{insulin AUC}_{\text{OGTT}}$$

Statistical analysis. Comparisons of experimental determinations between two groups in which the data were distributed normally were made with two-tailed *t* tests, and the rank-sum test was used for data that did not follow a normal distribution. Comparisons of more than two groups were made using ANOVA with post hoc tests to determine differences between specific groups. Within-group comparisons of poststimulus to basal values were made using repeated-measures ANOVA. Results are expressed as means ± SE unless otherwise noted.

RESULTS

Oral glucose tolerance test. The control (n = 14) and type 1 diabetic (n = 17) subjects had normal fasting glucose values that did not differ: 5.1 ± 0.07 and 5.3 ± 0.15 mmol/l, respectively (P = 0.17). In contrast, glucose values following glucose ingestion were significantly elevated in type 1 diabetic subjects relative to control subjects (Fig. 1*A*). The control group had a peak glucose level of 8.19 ± 0.59 mmol/l at 60 min, and plasma levels had returned to near basal by the end of the sampling period. The type 1 diabetic group had glucose concentrations that plateaued at 13.32 ± 0.36 mmol/l at 60 min, and there was no tendency for normalization of glycemia even at 120 min in the diabetic group. The glucose AUC during the OGTT was more than twice as large in the type 1 diabetic subjects relative to control subjects (265 ± 39.0 and 779 ± 39.4 mmol · l^{-1} · min^{-1}; $P < 0.001$).

Fasting insulin values were not different in the control and type 1 diabetic subjects (55.4 ± 5.1 and 82.6 ± 15.1 pmol/l, respectively; P = 0.13). Following glucose ingestion, insulin values were greater in the control subjects than in type 1 diabetic subjects at 30 and 60 min ($P < 0.05$), whereas values at 90 and 120 min were not different between the groups (Fig. 1*B*). Over the course of the OGTT, the insulin AUC was significantly greater in control subjects relative to type 1 diabetic subjects (31,134 ± 3,114 vs. 17,116 ± 2,532 pmol · l^{-1} · min^{-1}; P = 0.001). Similar results were observed in C-peptide AUC values (118 ± 15 vs. 61 ± 13 nmol · l^{-1} · min^{-1}; P = 0.007).

Fasting glucagon levels were similar in the control (n =

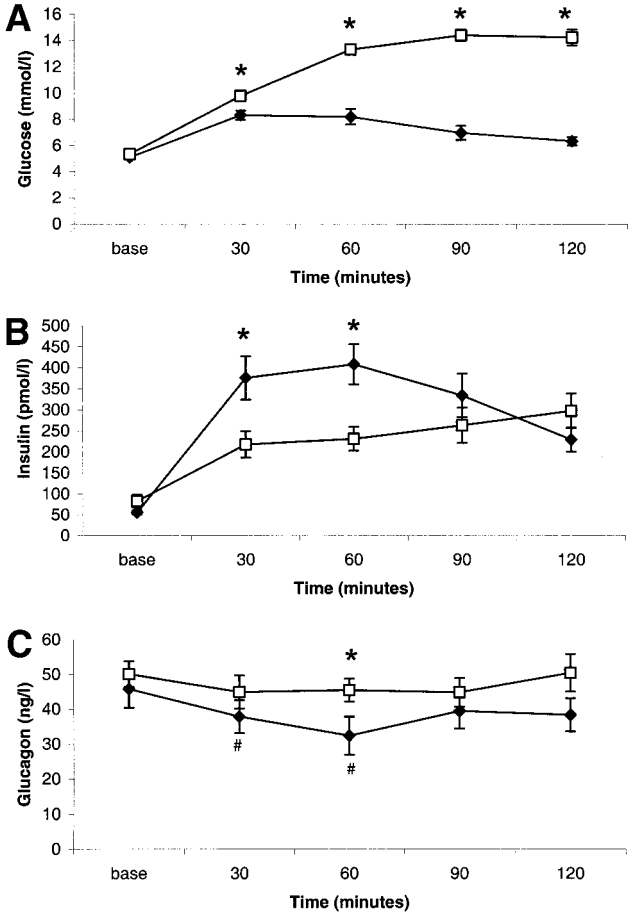

FIG. 1. Oral glucose tolerance test: glucose (*A*) and insulin (*B*) values in type 1 diabetic (□; n = 17) and control (◆; n = 14) subjects. *C*: Glucagon values in type 1 diabetic (□; n = 8) and control (◆; n = 10) subjects. *P < 0.05 between groups; #P < 0.05 from baseline.

10) and type 1 diabetic (n = 8) groups (50.1 ± 3.7 and 45.8 ± 5.4 ng/l, respectively; P = 0.54). Following glucose ingestion, there was a significant decrease in plasma glucagon at 30 and 60 min in the control group, but no change relative to fasting levels in the type 1 diabetic group. Consistent with a lack of suppression of glucagon in the type 1 diabetic subjects, the concentrations of glucagon relative to fasting levels were different between the two groups at 60 min (control subjects, 68 ± 6% of basal; type 1 diabetic subjects, 92 ± 4% of basal; $P < 0.05$) (Fig. 1*C*).

There were no differences in fasting or postprandial levels of GIP and GLP-1 between the control (n = 10) and type 1 diabetic (n = 8) groups. Basal levels of GIP were 23.4 ± 2.7 and 21.6 ± 2.3 pmol/l in the control and type 1 diabetic subjects, respectively, and the responses (AUC) following glucose ingestion were not different between the groups (1,674 ± 358 and 1,378 ± 165 pmol · l^{-1} · min^{-1}; P = 0.74). Fasting concentrations of GLP-1 were 9.3 ± 1.4 and 6.62 ± 0.76 pmol/l in the control and type 1 diabetic subjects, respectively (P = 0.15) and increased postprandially to a similar extent, with AUCs of 485 ± 70 and 677 ± 103 pmol · l^{-1} · min^{-1} (P = 0.12).

Incretin effect. Glucose values were well matched between the IVGTT and OGTT and equaled 103.1 ± 2 and 102.6 ± 2% in the control (n = 10) and type 1 diabetic (n =

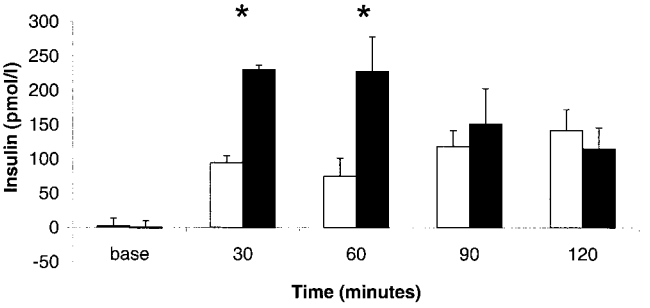

FIG. 2. Difference in insulin levels in response to oral and matched intravenous glucose load. □, type 1 diabetic subjects (n = 8); ■, control subjects (n = 10). *P < 0.05 between groups.

8) groups, respectively. In both the control and type 1 diabetic subjects, insulin release was significantly greater during oral glucose ingestion than during intravenous glucose administration. However, the incretin effect constituted a significantly higher percentage of postprandial insulin release in the control group, 70.3 ± 5.4%, compared with the type 1 diabetic group, 52.1 ± 5.9% (P = 0.03). The impairment of the incretin effect in the type 1 diabetic group was most pronounced at 60 min after glucose ingestion, when it was about half of the response in control subjects (control subjects, 57.7 ± 6%; type 1 diabetic subjects, 31.2 ± 6%; P = 0.01) (Fig. 2).

IVGTT. The acute insulin response to a glucose bolus (AIR_g) was diminished to a similar extent in both the type 1 diabetic (n = 8) and DPT (n = 8) subjects compared with control subjects (n = 10) (Fig. 3*A*), and this may have contributed to decreased rates of glucose disappearance (K_g) in these individuals (Table 1). S_I and S_G derived from the IVGTT data were not different among the three groups (Table 1). Fasting glucagon levels before the IVGTT were similar in the control, DPT, and type 1 diabetic subjects

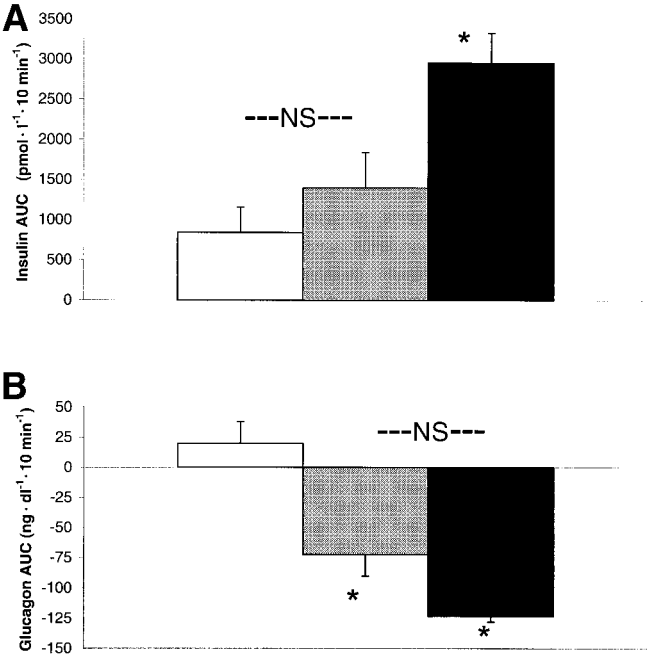

FIG. 3. Intravenous glucose tolerance test: insulin AUC (*A*) and glucagon AUC (*B*) values in type 1 diabetic (□; n = 8), DPT-1 (▩; n = 8), and control (■; n = 10) subjects. *P < 0.05 between groups.

TABLE 1
Frequently sampled intravenous glucose tolerance test

	Type 1 diabetic subjects	DPT-1 subjects	Control subjects	Type 1 diabetic vs. DPT-1 subjects (*P*)	Type 1 diabetic vs. control subjects (*P*)
n	8	8	11		
AIR_g (pmol/l)	91.3 ± 34.1	160.3 ± 50.3	329.1 ± 39.6	0.28	0.0005
K_g (%/min)	1.07 ± 0.19	1.44 ± 0.21	2.74 ± 0.52	0.22	0.02
S_g (min^{-1})	0.017 ± 0.002	0.015 ± 0.0028	0.022	0.68	0.30
S_I [$\times 10^{-5} \cdot (pmol/l)^{-1} \cdot min^{-1}$]	5.22 ± 1.17	6.78 ± 0.956	9.18 ± 1.59	0.32	0.08

Data are means ± SE.

(70.7 ± 5.7, 74 ± 2.0, and 68 ± 4.9 ng/l, respectively). Following intravenous glucose administration, glucagon levels were suppressed in the control and DPT groups (decremental AUC: –123.5 ± 18.7 and −72.3 ± 18 $ng \cdot l^{-1} \cdot min^{-1}$, respectively), but not in the type 1 diabetic subjects (19.9 ± 18.1 $ng \cdot l^{-1} \cdot min^{-1}$; $P < 0.05$ compared with control subjects) (Fig. 3*B*).

Insulin/glucose slope and glucose potentiation. Basal levels of glucose and insulin did not differ between the type 1 diabetic ($n = 8$) and control ($n = 10$) subjects, and AIR_{arg} at fasting glycemia was also similar in the two groups (Table 2). In contrast, the type 1 diabetic subjects showed much lower insulin secretion at each level of hyperglycemia. Thus, the insulin/glucose slope was significantly decreased in type 1 diabetic subjects (6.77 ± 1.72 pmol/l per mmol/l) relative to control subjects (30.2 ± 7.3 pmol/l per mmol/l; $P = 0.013$). In addition, the slope of glucose potentiation was also lower in the type 1 diabetic group (Table 2; Fig. 4). Finally, the AIR_{arg} at >22 mmol/l glucose (AIR_{max}) for the type 1 diabetic group was only 25% that of the control group (Table 2; Fig. 4).

DISCUSSION

This study reports a detailed investigation into the regulation of blood glucose in a unique group of subjects whose diabetes is best categorized as type 1 but is manifested solely by postprandial hyperglycemia (7). These subjects were identified through the screening and staging process for DPT-1 and thus have evidence of islet autoimmunity and an impairment of first-phase insulin secretion in response to glucose. However, in contrast to DPT-1 subjects who have nondiabetic glucose tolerance, the subjects we have characterized in these studies have marked hyperglycemia following an oral glucose load while having normal fasting glucose levels. Thus, the type 1 diabetic subjects represent a stage intermediate between the compensated glucose metabolism of the DPT-1 subjects and the totally uncompensated glucose metabolism of typical patients with type 1 diabetes. Both the DPT-1 subjects and the type 1 diabetic group we have described in this article are at high risk to progress to more severe, insulinopenic type 1 diabetes (7,18). This diabetes phenotype is novel and demonstrates that during the progression of autoimmune diabetes, normal fasting glucose can be maintained even in the face of a decrease in β-cell mass and a range of functional islet secretory defects.

We have demonstrated several parameters that potentially explain the disparity between fasting and postprandial glucose regulation in our type 1 diabetic group. As might be expected in the context of the serologic markers of β-cell autoimmunity, the type 1 diabetic subjects have evidence suggestive of a decrease in β-cell mass. The AIR_{arg} at glucose levels >22 mmol/l (AIR_{max}) has been shown in previous studies to correlate well with more direct assessments of β-cell number (13,19). The decrease of AIR_{max} in the type 1 diabetic subjects is consistent with the loss of a significant fraction of β-cells, likely from autoimmune destruction. In addition, the diabetic subjects described herein have normal function when measured at euglycemia but a marked decrease in function when measured at hyperglycemia. We have identified three other abnormalities that contribute to the abnormal OGTT. First, the β-cells in the type 1 diabetic subjects have a generally impaired responsiveness to glucose. Second, although the level of the incretin hormones GLP-1 and GIP are normal, the degree of augmented insulin secretion during oral glucose ingestion is below normal. Third, there is an abnormality in the suppression of glucagon during hyperglycemia in the type 1 diabetic group, which would tend to promote hyperglycemia.

As expected from the DPT-1 screening, the type 1 diabetic subjects had a markedly diminished FPIR as measured by AIR_g relative to control subjects. Furthermore, the insulin/glucose slope and the slope of potentiation, measures of the effectiveness of glucose to augment insulin secretion in the presence of other secretagogues

TABLE 2
Glucose potentiation

	Type 1 diabetic subjects	Control subjects	*P*
n	8	10	
Fasting AIR_{arg} (pmol/l)	193 ± 61.3	264 ± 33.5	0.30
AIR_{max} (pmol/l)	629 ± 159	2524 ± 413	0.0013
Slope insulin/glucose (pmol/l per mmol/l)	6.77 ± 1.72	30.2 ± 7.3	0.013
Slope glucose potentiation (pmol/l per mmol/l)	30.2 ± 6.1	102 ± 18.7	0.005

Data are means ± SE.

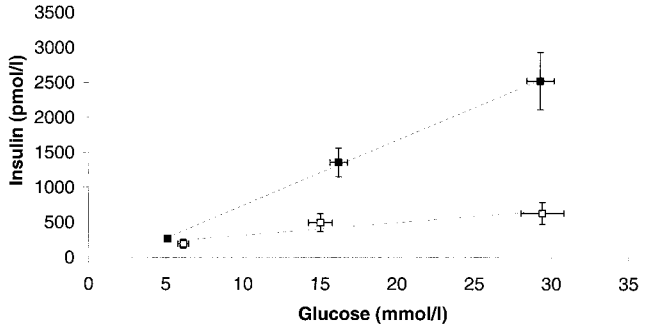

FIG. 4. Slope of glucose potentiation: AIR_{arg} at clamped glucose concentrations. □, type 1 diabetic subjects ($n = 8$); ■, control subjects ($n = 10$).

(13), were also significantly impaired in these individuals. However, since the acute insulin response to arginine at basal glucose was not different in these subjects relative to control subjects, it appears that their response to some nonglucose stimuli remains intact. The disproportionate defect in the insulin response to glucose in the type 1 diabetic subjects bears some similarity to the secretory abnormalities characteristic of type 2 diabetes (20), a condition in which β-cell dysfunction rather than β-cell loss is thought to be the primary pathology. This suggests that beyond islet cell destruction, the autoimmune process active in the type 1 diabetic subjects leads to functional compromise of the remaining β-cells. The presence of functional alterations in insulin secretion, in addition to β-cell loss, has been previously proposed in animal models (21) and in a small number of subjects with typical type 1 diabetes (22).

Insulin secretion following glucose ingestion was attenuated in the first hour of the OGTT in the type 1 diabetic subjects and increased only as plasma glucose levels became abnormally elevated. In addition, the type 1 diabetic group had a significant decrease in the incretin effect that was also most prominent in the first part of the OGTT. The incretin effect, the insulinotropic actions of gastrointestinal hormones and neural stimuli to augment the β-cell response beyond glycemic stimulation alone, has been estimated to account for 60–70% of the insulin secreted after oral glucose ingestion in healthy humans (10,23), similar to what we observed in our group of control subjects. Much of the incretin effect has been attributed to the actions of GIP and GLP-1, which are secreted from endocrine cells in the gut following glucose ingestion (23,24). Since the type 1 diabetic subjects have postprandial GIP and GLP-1 responses that are not different from control subjects, we infer that secretion of the incretin hormones is not abnormal in these individuals. Because the incretin effect is calculated using a within-subject comparison, this abnormality in the type 1 diabetic subjects cannot be explained simply by a decrease in β-cell mass and is likely due to a functional abnormality of the β-cell. Although our results do not provide direct evidence as to the cause of the decreased incretin effect in the type 1 diabetic group, there are several possibilities worth considering. These include generalized impairment of the β-cell, a selective defect in the response to GIP and/or GLP-1, or a defect in the response to stimulatory neural signals activated by glucose ingestion. The incretin effect was not completely abolished in these subjects, as has been described for people with type 2 diabetes (25). Nonetheless, we believe that the relative impairment in the incretin response, especially in the first 60 min of the OGTT, is an important contribution to the postprandial hyperglycemia in these individuals.

Besides the profile of β-cell dysfunction that we have documented in type 1 diabetic subjects, they also appear to have a defect in α-cell regulation. Whereas fasting glucagon levels in type 1 diabetic subjects were comparable to control and DPT-1 subjects, there was a significant impairment in the suppression of glucagon levels in response to hyperglycemia in the type 1 diabetic group. This abnormality was apparent following either oral or intravenous glucose loading. While such a defect is known to occur in long-standing type 1 diabetes, our data demonstrate that glucagon regulation is impaired at an early stage of the disease, even when modest insulin secretory capability is present. There are several possible explanations that fit these data. First, a primary alteration of α-cell function caused by the autoimmune process may be present in type 1 diabetes. Alternatively, the insulin-mediated suppression of α-cell secretion may be abnormal either because of lower intra-islet insulin levels or because the autoimmune milieu attenuates the paracrine effects of the secreted insulin. Although elevations in plasma glucagon do not have a measurable effect on postprandial glycemia in healthy humans (26), the contribution of abnormal glucagon suppression to glucose intolerance in diabetic subjects has been reported (27–29). We do not think the persistence of basal glucagon levels during the OGTT is likely to be the primary factor in the postprandial glycemic pattern in our type 1 diabetic subjects. However, as previously suggested (27–29), it is reasonable to believe that the relative hyperglucagonemia during the OGTT in the type 1 diabetic group contributes to their hyperglycemia, probably through persistent stimulation of hepatic glucose production.

Because of restrictions in access to subjects enrolled in the DPT-1, we were not able to perform incretin or glucose potentiation studies on this group. However, a more thorough examination of DPT-1 subjects would be very informative in discerning the relationship of the abnormalities we have described in type 1 diabetic subjects and oral glucose tolerance. One could speculate that AIR_{max} values in the DPT-1 group would fall between those of normal subjects and the type 1 diabetic group, suggesting that those antibody-positive subjects with normal glucose tolerance may simply have lost fewer islet cells than others. Alternatively, it may be that there are functional differences in β-cell secretion that contribute to postprandial hyperglycemia in groups of subjects with similar levels of islet autoimmunity. Based on the marked difference in OGTT between type 1 diabetic and DPT-1 subjects, and the defective incretin effect with type 1 diabetic subjects, we hypothesize that the incretin response in the latter group would have been closer to normal. This and other hypotheses will be tested in future studies, but our current findings indicate that there is heterogeneity in islet cell function among individuals with previous or ongoing islet autoimmunity.

The metabolic responses described in the type 1 dia-

betic population are similar to subjects with type 1 diabetes who have a transient remission (or honeymoon) period (30–33). Diabetic patients who have a honeymoon phase can maintain normal HbA_{1c} without insulin therapy for periods of months to years. Similar to our subjects, they continue to have very low or absent C-peptide responses to intravenous or oral glucose, yet they have normal responses to intravenous arginine and glucagon stimulation (30–33). To our knowledge, the incretin effect has not been measured in type 1 diabetic subjects during the honeymoon phase of their disease. A common feature of both our type 1 diabetic patients and those in the honeymoon phase is the absence of fasting hyperglycemia, which may facilitate effective β-cell function in the face of diminished β-cell mass. Alternatively, it is possible that the observed β-cell responses in both our type 1 diabetic patients and those in the honeymoon phase reflect a quiescence in the inflammatory activity surrounding the islet.

Interestingly, the OGTT responses of the type 1 diabetic subjects share some general features of classic impaired glucose tolerance and type 2 diabetes as well as other forms of nonautoimmune diabetes. The islet cell abnormalities in the type 1 diabetic group are similar in many respects to the characteristics of islet function in persons with impaired glucose tolerance (34,35) and type 2 diabetes. That is, a disproportionate loss of β-cell sensitivity to glucose, an impaired incretin effect, and dysregulation of glucagon release have all been previously described in type 2 diabetes (19,25) and are thought to contribute to glucose intolerance in those patients. However, there are important differences in our type 1 diabetic subjects and people with type 2 diabetes. The discrepancy between fasting glucose levels and postprandial glucose levels is much higher in type 1 diabetic than in type 2 diabetic subjects, where fasting glucose levels tend to increase in parallel with worsening glucose tolerance (36,37). In addition, whereas insulin resistance is a hallmark of type 2 diabetes (38), and several reports suggest that glucose effectiveness is impaired in these patients as well (39,40), these parameters did not differ among type 1 diabetic, control, or DPT-1 subjects in the present study. These type 1 diabetic subjects are also clearly distinct from individuals with maturity-onset diabetes of the young (MODY), another group of young subjects with mild diabetes stemming primarily from β-cell dysfunction. Individuals with mutations that classify them as having MODY1 and -2 typically have fasting hyperglycemia in addition to abnormal glucose tolerance, and MODY2 subjects have a decrease β-cell sensitivity to glucose as a result of mutations in the glucokinase gene (41). Thus, clear differences in metabolic physiology can be demonstrated among type 1 diabetic subjects and other groups that share general phenotypic characteristics. Such heterogeneity emphasizes the value of in vivo characterization in the pursuit of the pathogenesis of different diabetic syndromes.

In summary, we have characterized important parameters of glucose tolerance in subjects with type 1 diabetes in whom hyperglycemia in response to oral glucose is the sole abnormality. These subjects demonstrate apparently normal islet function in the fasting state but show marked abnormalities in response to a glucose challenge. Not only is the β-cell response to hyperglycemia impaired, there is also a decreased incretin effect and a defect in the suppression of glucagon levels. It is possible that the ability of these subjects to maintain normal fasting glucose in the face of marked β-cell secretory abnormalities is at least in part due to their normal insulin sensitivity. These data demonstrate a novel profile of abnormalities in glucose regulation in a group of subjects that we propose have an intermediate, or early, stage of type 1 diabetes. These findings emphasize the gradations that are present in the phenotypic expression of type 1 diabetes and identify some of the more proximal functional abnormalities that occur with islet autoimmunity. The heterogeneity in islet cell function among subjects classified as having type 1 diabetes will need to be carefully considered in the design of future intervention trials.

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