Insulin Intervention in Slowly Progressive Insulin-Dependent (Type 1) Diabetes Mellitus

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Objective: We tested the hypothesis that insulin therapy rather than sulfonylurea (SU) treatment is preferable to reverse or preserve β-cell function among patients with slowly progressive insulin-dependent (type 1) diabetes (SPIDDM) or latent autoimmune diabetes in adults.

Methods: This multicenter, randomized, nonblinded clinical study screened 4089 non-insulin-dependent diabetic patients for glutamic acid decarboxylase autoantibodies (GADAb). Sixty GADAb-positive non-insulin-requiring diabetic patients with a 5-yr duration or shorter of diabetes were assigned to either the SU group (n = 30) or the insulin group (n = 30). Serum C-peptide responses to annual oral glucose tolerance tests were followed up for a mean of 57 months. The primary endpoint was an insulin-dependent state defined by the sum of serum C-peptide values during the oral glucose tolerance test (ΣC-peptide) less than 4 ng/ml (1.32 nmol/liter).

Results: The progression rate to an insulin-dependent state in the insulin group (three of 30, 10%) was lower than that in the SU group (13 of 30, 43%; $P = 0.003$, log-rank). Longitudinal analysis demonstrated that ΣC-peptide values were better preserved in the insulin group than in the SU group. Multiple regression analysis demonstrated that insulin treatment, a preserved C-peptide response, and a low GADAb titer at entry were independent factors in preventing progression to an insulin-dependent state. Subgroup analysis suggested that insulin intervention was highly effective for SPIDDM patients with high GADAb titers [$\geq$10 U/ml (180 World Health Organization U/ml)] and preserved β-cell function [ΣC-peptide $\geq$ 10 ng/ml (3.31 nmol/liter)] at entry. No severe hypoglycemic episodes occurred during the study.

Conclusions: Insulin intervention to preserve β-cell function is effective and safe for patients with SPIDDM or latent autoimmune diabetes in adults. **(*J Clin Endocrinol Metab* 93: 2115–2121, 2008)**

Residual insulin secretion in type 1 diabetes contributes to stable glycemic control and inhibits the occurrence of diabetic complications (1). It, therefore, is an important goal to preserve β-cell function in any intervention strategy of patients with type 1 diabetes (2). Slowly progressive insulin-dependent (type 1) diabetes (SPIDDM) (3–9) [also referred to as latent autoimmune diabetes in adults (LADA) (10)] is characterized by the clinical phenotype of late-onset type 2 diabetes. Progressive β-cell failure that leads to insulin dependence over several years and persistent islet-cell autoantibodies such as glutamic acid decarboxylase autoantibodies (GADAb) and islet-cell antibodies (ICA) are other characteristics. One risk factor for the progres-

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Abbreviations: BMI, Body mass index; DPT-1, Diabetes Prevention Trial-1; FBG, fasting blood glucose; GADAb, glutamic acid decarboxylase autoantibodies; 2-h BG, blood glucose levels at 2 h during OGTT; HbA_{1c}, glycosylated hemoglobin; HLA, histocompatibility leucocyte antigen; ICA, islet-cell antibodies; LADA, latent autoimmune diabetes in adults; NPH, neutral-protamine-Hagedorn; OGTT, oral glucose tolerance test; SPIDDM, slowly progressive insulin-dependent (type 1) diabetes; SU, sulfonylurea.

sion of β-cell failure in SPIDDM is sulfonylurea (SU) (9). We postulated that insulin therapy instead of SU can reverse or preserve β-cell function in patients with SPIDDM. A pilot study of early insulin administration instead of SU in ICA-positive SPIDDM has demonstrated improved β-cell function with negative conversion of ICA (11). These results suggest that early insulin treatment can prevent or delay the progression of β-cell failure in SPIDDM. We organized a multicenter randomized clinical trial (Tokyo Study) (12, 13) to examine the ability of insulin to prevent progressive β-cell dysfunction in SPIDDM.

Patients and Methods

Patient eligibility

Patients who met the criteria for diabetes mellitus (14) and who were not treated with insulin at seven hospitals in the Tokyo area were screened for GADAb between January 20, 1996, and June 20, 2001. Those patients with GADAb in at least two consecutive serum samples taken within 1 month were further evaluated to determine suitability for enrollment. The inclusion criteria were that patients should use SU agents to obtain good glycemic control as described below, and the duration of diabetes should be within 5 yr from onset (or diagnosis). Exclusion criteria were a history of hyperglycemia requiring insulin and/or a history of ketosis or ketoacidosis. Patients with malignant diseases, systemic inflammatory diseases, renal or liver disorders, or malabsorption were also excluded. Eligible patients were randomly assigned using a centralized, masked-draw system to receive sc injections of insulin (insulin group) or oral SU (SU group).

Study protocol

All enrolled participants received diet therapy according to food exchange lists (15). Those assigned to the insulin group ceased using oral hypoglycemic agents 2 d before starting insulin therapy. Target glycemic levels were defined as fasting blood glucose (FBG) less than 120 mg/dl (6.7 mmol/liter), postprandial blood glucose levels less than 200 mg/dl (11.1 mmol/liter), and HbA_{1c} levels less than 7.0%. Subcutaneous insulin administration to the insulin group patients began with a daily dose of 2–4 U neutral-protamine-Hagedorn (NPH) insulin (Novolin N; Novo Nordisk, Copenhagen, Denmark) in the morning. The dosage was adjusted during each hospital visit to achieve target glycemic levels. When the target could not be achieved by a single injection of NPH insulin, twice-daily (before morning and evening meals) injections of NPH insulin were administered, increasing the dose of insulin by 2 U. If this strategy did not achieve the target, NPH insulin was replaced with premixed insulin (Novolin 30R; Novo Nordisk) twice daily plus a premeal regimen of regular insulin (Novolin R; Novo Nordisk), increasing the dose of insulin by 2 U. When the C-peptide response of the patients in the insulin group progressed to an insulin-dependent state as defined below, a multiple insulin injection regimen (premeal injection of regular insulin plus NPH insulin at bedtime) was started.

Follow-up assessments and endpoint

Levels of FBG and glycosylated hemoglobin (HbA_{1c}) were measured at baseline and every 3 months during the follow-up period. Dosages of insulin or SU in each group were adjusted to obtain predetermined glycemic levels during the study. Only oral hypoglycemic agents administered to the SU group comprised either gliclazide (20 or 40 mg/d) or glibenclamide (1.25–7.5 mg/d). The patients in the SU group were judged to have reached a stage of secondary failure of SU agents when FBG levels exceeded 200 mg/dl and/or HbA_{1c} levels exceeded 9.0% despite the use of a maximum dose of glibenclamide (7.5 mg/d) (16). Patients in the SU group were switched to a multiple insulin injection regimen when they reached the stage of secondary failure of SU agents. Residual β-cell function was evaluated by an annual 75-g oral glucose tolerance test (OGTT). Patients underwent an OGTT after a 12-h fast without receiving their morning injection of insulin or dose of SU. Residual β-cell function was assessed by the sum of serum C-peptide values at 0, 30, 60, 90, and 120 min during the OGTT (ΣC-peptide). Patients whose ΣC-peptide levels fell to less than 4 ng/ml (1.32 nmol/liter) were defined as being in an insulin-dependent state because studies on the natural history of C-peptide levels in SPIDDM have demonstrated that all patients whose ΣC-peptide levels reach less than 4 ng/ml require insulin and are ketosis prone (3, 4, 11). The primary endpoint was the time when the ΣC-peptide levels of patients indicated an insulin-dependent state (ΣC-peptide < 4 ng/ml). Chemical hypoglycemia was defined as a blood glucose level of less than 60 mg/dl (3.3 mmol/liter) irrespective of hypoglycemic symptoms. Severe hypoglycemia was defined as loss of consciousness, convulsion, stupor, or hypoglycemia requiring assistance of another person or iv glucose. All patients were instructed to self-monitor their blood glucose levels before and 2 h after meals and at bedtime at least once a week.

Laboratory measures

Levels of GADAb were measured by immunoprecipitation (Cosmic Co., Tokyo, Japan) and GADAb titers of 1.5 U/ml (mean + 3 SD of normal controls) or higher were judged as positive (17). Insulin autoantibodies and serum C-peptide levels were measured (18, 19).

Sample size

Based on our previous study (11), the estimated 2.5-yr incidence of progression to an insulin-dependent state was 40 and 0% in patients with SPIDDM treated with SU and with insulin, respectively. Thus, a total of 21 patients in each group were required to provide a 90% power to detect a difference of this magnitude over a follow-up period of 2.5 yr. To allow for an unpredictable number of withdrawals, we enrolled 60 patients with the expectation that at least 21 patients would be left in each group after 5 yr of follow-up.

Ethics

Each institutional review board approved the protocol, and all patients provided written informed consent to participate.

Statistical analysis

Data were analyzed according to the intention-to-treat principle. To evaluate the difference in longitudinal C-peptide data between the insulin and SU groups, the interaction between time and treatment assignment at entry (insulin or SU) was examined using repeated-measures ANOVA. Interaction among time, treatment assignment, and subgroup based on baseline characteristics was also analyzed using repeated-measures ANOVA on C-peptide values. Categorical variables were compared using Fisher's exact test. Differences in continuous variables between the two groups were compared using the Mann-Whitney *U* test, and longitudinal changes of continuous variables except for C-peptide values in each group were analyzed using the Wilcoxon signed rank test. We defined body mass index (BMI) as weight in kilograms divided by the square of height in meters. Levels of GADAb showed heterogeneity of variance and were therefore log-transformed for analysis and back-transformed for presentation. Kaplan-Meier life tables were constructed and compared using the log-rank χ^2 statistic. We estimated multiple hazard ratios of covariates for progression to an insulin-dependent state using a Cox proportional-hazards regression analysis with or without stepwise selection. A stringency level (*P* value) of 0.05 was used both to include and exclude variables in the stepwise selection. Tests of significance were two tailed. Statistical analyses were performed using JMP. Values are expressed as means ± SD except as otherwise described.

Results

Patients

Among 4089 patients with diabetes treated with SU, 212 had GADAb in two consecutive serum samples and 128 had diabetes for more than 5 yr. A total of 72 patients were eligible for enrollment in our study and written informed consent was obtained from 61 patients to participate in this study. One patient was lost between enrollment and entry, resulting in 60 patients being randomly allocated to either the insulin or the SU group. None of these patients was lost during the study, which proceeded for 57 ± 7 months (range, 36–60 months) of follow-up. The baseline characteristics between the two groups did not significantly differ (Table 1).

Progression rate to insulin dependence

Thirteen (43%) and three (10%) patients in the SU and insulin groups, respectively, progressed to an insulin-dependent state. The proportion of participants who progressed to an insulin-dependent state, when averaged annually over follow-up was 11 and 2% per annum in the SU and insulin groups, respectively. The cumulative probability of progression to an insulin-dependent state significantly differed between the groups ($P = 0.003$, log-rank test) (Fig. 1).

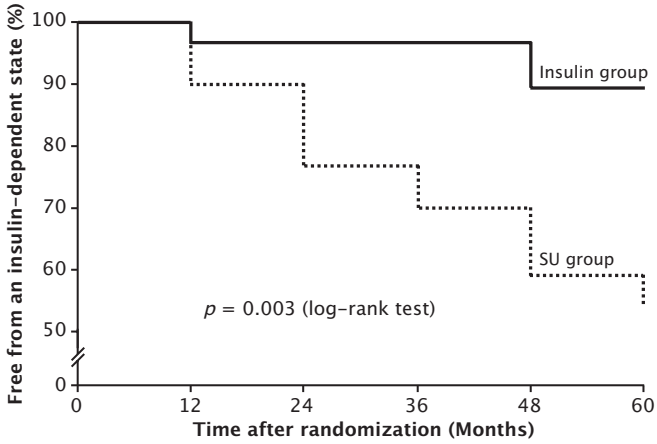

FIG. 1. Kaplan-Meier life table analysis showing proportion of patients with SPIDDM who were free from an insulin-dependent state. Insulin group were SPIDDM patients who were allocated to insulin treatment at entry, and the SU group included SPIDDM patients who were allocated to SU therapy at entry.

Risk factors for progression to an insulin-dependent state

Treatment (SU or insulin), titer of GADAb at entry, and preserved C-peptide value at entry independently affected progression to an insulin-dependent state (Table 2). Based on these and previous results (20), patients from both groups were subclassified according to titers of GADAb and ΣC-peptide values as

TABLE 1. Baseline characteristics of GADAb-positive patients with SPIDDM

At entry	Insulin group (n = 30)	SU group (n = 30)	*P* value (insulin group *vs.* SU group)
Age (yr)	54 ± 13	51 ± 13	0.39
Sex (n)			
Male	17	16	1.00
Female	13	14	
Duration of diabetes (yr)	1.7 ± 1.9	1.9 ± 1.7	0.55
Treatment for diabetes mellitus before entry			
Gliclazide, n (%)[a]	18 (60)	18 (60)	1.00
Glibenclamide, n (%)[b]	12 (40)	12 (40)	
Family history of type 2 diabetes, n (%)	12 (40)	15 (50)	0.60
BMI (kg/m^2)	20.4 ± 2.6	21.7 ± 4.0	0.25
GADAb (U/ml)	34.6 ± 12.7	17.1 ± 8.3	0.35
FBG (mg/dl)	133 ± 26	135 ± 26	0.64
HbA_{1c} (%)	7.4 ± 1.7	7.3 ± 1.8	0.30
2-h BG (mg/dl)	288 ± 99	292 ± 101	0.85
Fasting serum C-peptide (ng/ml)	1.86 ± 1.02	1.77 ± 0.90	0.84
ΣC-peptide (ng/ml)	20.37 ± 14.96	19.55 ± 9.45	0.55
HLA			
DR4, n (%)[c]	18 (60)	17 (57)	1.00
DR9, n (%)	9 (30)	12 (40)	0.59
DR2, n (%)[c]	5 (17)	6 (20)	1.00
IAA, n (%)	6 (20)	6 (20)	1.00
Dose of insulin (U/kg·d)	0.13 ± 0.11		

Unless indicated otherwise, results are shown as means ± SD. Σ C-peptide is the sum of serum C-peptide values during OGTT at 0, 30, 60, 90, and 120 min. To convert values for glucose to mmol/liter, multiply by 0.05551; to convert values for C-peptide to nmol/liter, multiply by 0.331. IAA, Insulin autoantibodies.

[a] Mean dose and frequency of gliclazide in the insulin group were 20 mg/d and 1.0/d, respectively, and in the SU group were 24 mg/d (not significant *vs.* insulin group) and 1.1/d (not significant *vs.* insulin group), respectively.

[b] Mean dose and frequency of glibenclamide in insulin group were 4.3 mg/d and 1.3/d, respectively, and in SU group were 3.6 mg/d (not significant *vs.* insulin group) and 1.2/d (not significant *vs.* insulin group), respectively.

[c] Prevalence of HLA-DR4 and -DR2 in all patients was higher and lower, respectively, when compared with nondiabetic controls (n = 210; age, 53 ± 10 yr; sex, 107 males and 103 females) [DR4, 40% (84 of 210), $P = 0.01$; DR2, 33% (70 of 210), $P = 0.03$].

TABLE 2. Results of Cox's regression multivariate analysis of progression to insulin-dependent state

Variable	Multivariate analysis		Multivariate analysis stepwise selection	
	Hazard ratio (95% CI)[a]	*P* value	Hazard ratio (95% CI)[a]	*P* value
Insulin treatment	0.008 (4×10^{-5} to 0.093)	<0.001	0.153 (0.055–0.342)	<0.001
Titer of GADAb (U/ml)	595.3 (11.05–4.5×10^{6})	<0.001	3.244 (1.679–6.909)	<0.001
Σ C-peptide (ng/ml)	2×10^{-6} (5×10^{-13} to 0.003)	<0.001	0.008 (2×10^{-4} to 0.086)	<0.001
Age (yr)	0.153 (0.003–1.184)	0.08	Eliminated	
Male	1.147 (0.377–3.496)	0.80	Eliminated	
Duration of diabetes (months)	0.976 (0.114–9.920)	0.98	Eliminated	
Family history of type 2 diabetes	0.455 (0.034–2.139)	0.39	Eliminated	
BMI (kg/m^2)	42.76 (2.081–2.0×10^{4})	0.01	Eliminated	
FBG (mg/dl)	2.657 (0.635–17.71)	0.19	Eliminated	
HbA_{1c} (%)	0.149 (0.013–0.685)	0.01	Eliminated	
2-h BG (mg/dl)	6.029 (0.858–121.4)	0.07	Eliminated	
Fasting serum C-peptide (ng/ml)	0.371 (0.006–5.978)	0.59	Eliminated	
HLA-DR4	0.178 (0.009–1.061)	0.06	Eliminated	
HLA-DR9	0.565 (0.065–3.123)	0.53	Eliminated	
HLA-DR2	2.218 (0.327–20.29)	0.42	Eliminated	
IAA	1.016 (0.165–9.647)	0.99	Eliminated	

Titers of GADAb were log transformed and analyzed. Σ C-peptide is the sum of serum C-peptide values during OGTT at 0, 30, 60, 90, and 120 min. CI, Confidence interval; IAA, insulin autoantibodies.

[a] Standard hazard ratios for continuous variables are expressed per SD increase for each factor. Reference group for hazards ratios for dichotomous variables included patients without the respective factor.

follows: group A, high titer of GADAb (≥10 U/ml) and high degree of preserved β-cell function [ΣC-peptide ≥ 10 ng/ml (3.31 nmol/liter)] at entry; group B, high titer of GADAb (≥10 U/ml) and low degree of preserved β-cell function (ΣC-peptide < 10 ng/ml) at entry; group C, low titer of GADAb (< 10 U/ml) and high degree of preserved β-cell function (ΣC-peptide ≥ 10 ng/ml) at entry; group D, low titer of GADAb (<10 U/ml) and low degree of preserved β-cell function (ΣC-peptide < 10 ng/ml) at entry. However, none of our patients fits the criteria for group D. The cutoff titer of GADAb at 10 U/ml (21 SD above the mean of normal controls) for subgroups was established from receiver-operating characteristic curve analysis in another study (20). Calibration of the GADAb titer using the World Health Organization (WHO) standards established at the Diabetes Antibody Standardization Program 2002 showed that a titer of 10 U/ml in our assay corresponded to 180 WHO U/ml.

Among the patients in group A, 67% (eight of 12) and none in the SU and insulin groups, respectively, progressed to an insulin-dependent state ($P < 0.001$; Fig. 2). The frequencies of progression to an insulin-dependent state did not significantly differ between groups B and C regardless of treatment (Fig. 2).

Longitudinal changes in C-peptide response to OGTT and GADAb titer

The C-peptide responses to OGTT progressively decreased in the SU group (Fig. 3A). In contrast, the C-peptide value in the insulin group increased at 12 and decreased at 24 months, and the values remained unchanged for up to 60 months. Repeated-measures ANOVA revealed a significant time-by-treatment-assignment interaction in all patients ($P = 0.005$; Fig. 3A) and in group A patients ($P = 0.04$; Fig. 3B) but not in group C ($P = 0.09$; Fig. 3C). No significant interaction among time, treatment, and subgroup was evident. All data from the SU group, including those with secondary failure of oral hypoglycemic agents and those who had been switched from SU to insulin, were included in this analysis.

The titers of GADAb at the completion of the study in the insulin group (11.7 ± 29.0 U/ml) and the SU group (7.0 ± 6.0 U/ml) were significantly decreased compared with baseline values (Table 1) ($P = 0.001$ and $P < 0.001$, respectively). Titers of GADAb did not significantly differ between these two groups during the study.

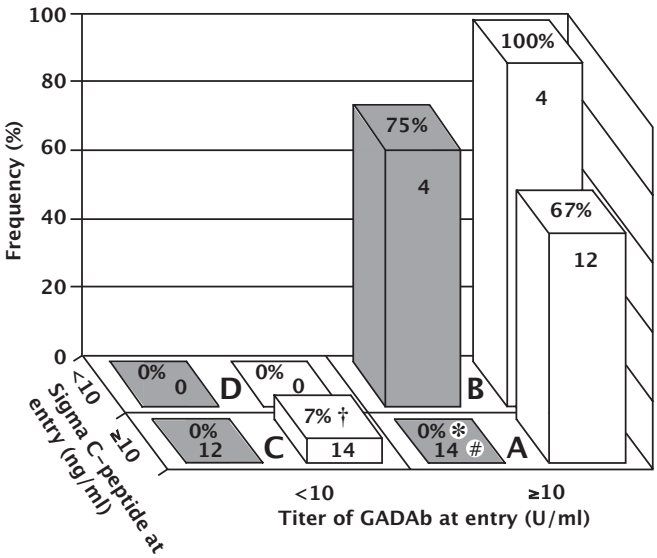

FIG. 2. Three-dimensional display of frequency of patients that progressed to an insulin-dependent state in both insulin (*shaded columns*) and SU (*white columns*) groups according to C-peptide responses to oral glucose and GADAb titer at entry. A, Group A [GADAb ≥ 10 U/ml and ΣC-peptide ≥ 10 ng/ml [3.31 nmol/liter)]; B, group B (GADAb ≥10 U/ml and ΣC-peptide < 10 ng/ml); C, group C (GADAb < 10 U/ml and ΣC-peptide ≥ 10 ng/ml); D, group D (GADAb < 10 U/ml and ΣC-peptide < 10 ng/ml). *Numbers on columns* indicate numbers of patients in each subgroup. *, $P < 0.001$ *vs.* group A of SU group; #, $P = 0.005$ *vs.* group B of insulin group; †, $P = 0.003$ *vs.* group A of SU group.

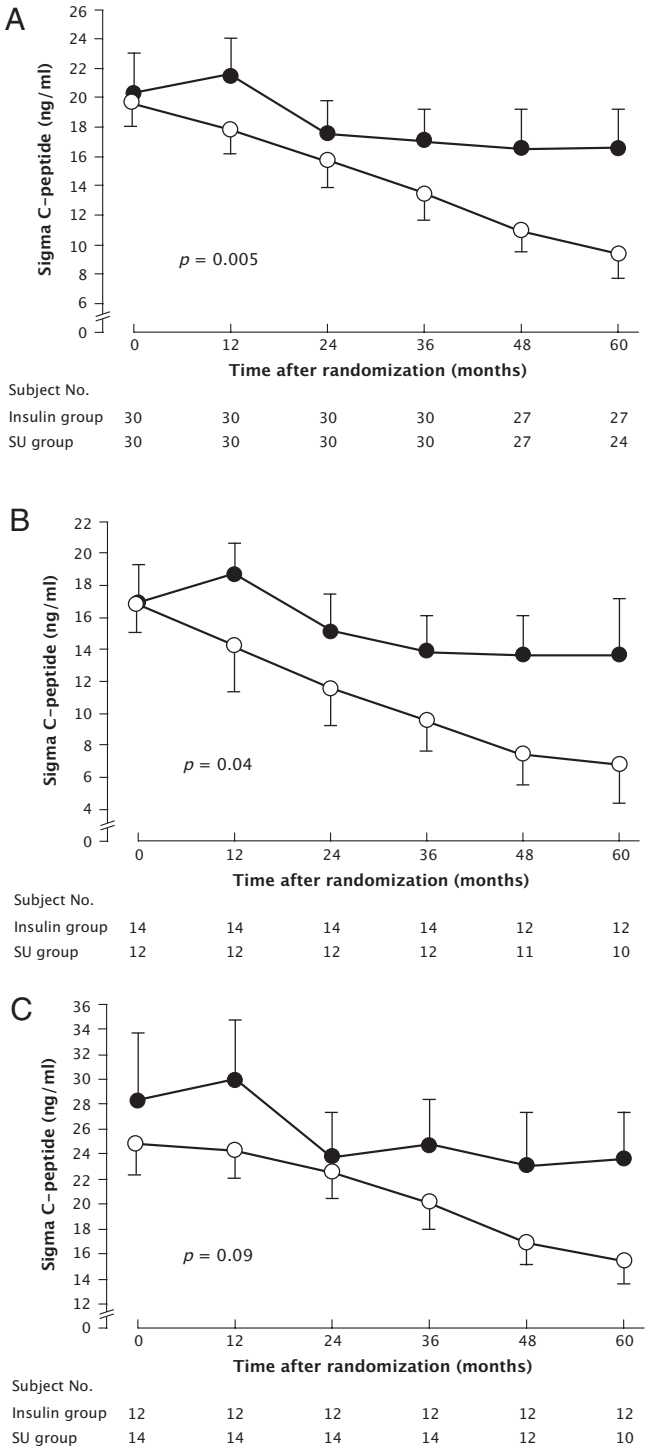

FIG. 3. A, Longitudinal changes in C-peptide responses to 75-g oral glucose in insulin (●) and SU (○) groups. Data are expressed as means ± SEM. Repeated-measures ANOVA revealed a significant interaction between time and treatment assignment (SU or insulin) ($F = 3.9$; $P = 0.005$). Multiply by 0.331 to convert C-peptide values to nanomoles per liter. B, Results of group A [GADAb ≥ 10 U/ml and ΣC-peptide ≥ 10 ng/ml (3.31 nmol/liter)], longitudinal changes in C-peptide responses to 75 g oral glucose in insulin (●) and SU (○) groups. Data are expressed as means ± SEM. Repeated-measures ANOVA revealed a significant interaction between time and treatment assignment (SU or insulin) ($F = 3.1$; $P = 0.04$). Multiply by 0.331 to convert C-peptide values to nanomoles per liter. C, Results of group C [GADAb < 10 U/ml and ΣC-peptide ≥ 10 ng/ml (3.31 nmol/liter)], longitudinal changes in C-peptide responses to 75 g oral glucose in insulin (●) and SU (○) groups. Data are expressed as means ± SEM. Repeated-measures ANOVA showed no significant interaction between time and treatment assignment (SU or insulin) ($P = 0.09$). Multiply by 0.331 to convert C-peptide values to nanomoles per liter.

Changes in treatment and insulin dose

Fourteen (47%) patients in the SU group had to change to insulin injections because of secondary failure of the SU agents. Thirteen of these 14 patients (93%) progressed to an insulin-dependent state. All patients who experienced secondary failure of SU agents were changed to insulin a mean of 4 months before reaching an insulin-dependent state. The insulin dosage administered to patients in the SU group was 0.61 ± 0.19 U/kg·d at the end of the study ($P < 0.001$ *vs.* insulin group with 0.32 ± 0.27 U/kg·d). The insulin dose given to the insulin group at the end of study was increased ($P < 0.001$ *vs.* baseline).

Changes in BMI, HbA_{1c}, FBG, and blood glucose levels at 2 h during OGTT (2-h BG)

The BMI of the insulin and SU groups was significantly increased at the completion of the study (21.3 ± 2.5 kg/m^2, $P = 0.001$, and 22.8 ± 4.1 kg/m^2, $P = 0.002$ *vs.* baseline, respectively). The HbA_{1c} levels at the end of the follow-up (insulin group, 7.2 ± 1.6%; SU group, 7.7 ± 1.4%) did not significantly differ from those at baseline. The 2-h BG levels were significantly increased at the completion of study in both groups [insulin group: 352 ± 107 mg/dl (19.5 ± 5.9 mmol/liter), $P = 0.004$ *vs.* baseline; SU group: 388 ± 116 mg/dl (21.5 ± 6.4 mmol/liter), $P < 0.001$ *vs.* baseline]. The FBG value at 60 months in the SU group [184 ± 65 mg/dl (10.2 ± 3.6 mmol/liter)] was significantly increased compared with baseline ($P < 0.001$), whereas that in the insulin group [153 ± 59 mg/dl (8.5 ± 3.3 mmol/liter)] was not. The FBG value at 60 months in the insulin group was lower than that in the SU group ($P = 0.04$). Levels of BMI, HbA_{1c}, and 2-h BG did not significantly differ between the two groups during the study.

Hypoglycemia

The mean frequency of chemical hypoglycemia was 0.8 (95% confidence interval, 0.0–1.6) and 2.4 (1.1–3.7) per person-year in the insulin and SU groups, respectively, during the study period ($P = 0.12$). Severe hypoglycemia in either group was not documented during the study.

Discussion

Our study demonstrates that insulin intervention is effective and safe for treating gradual β-cell failure especially in patients with SPIDDM whose β-cell function is preserved (ΣC-peptide ≥ 10 ng/ml) and who have a high titer of GADAb [≥10 U/ml (180 WHO U/ml)] at the start of insulin therapy. A high GADAb titer (≥10 U/ml) in SPIDDM is a marker for both activated T cell response to β-cell destruction and a high risk for progression to insulin dependence (21, 22). Both the SU and the insulin group patients with a low GADAb titer (GADAb < 10 U/ml) and preserved β-cell function (ΣC-peptide ≥ 10 ng/ml) at entry might be expected to progress very slowly to an insulin-dependent state. Therefore, the effect of insulin intervention to prevent further progression of β-cell dysfunction in this subgroup of patients could not be demonstrated. If patients with a low GADAb titer and preserved β-cell function at entry were observed for a longer

period, the preventive effect of insulin intervention should become even more apparent in this subgroup. Insulin intervention to sustain β-cell function is clinically important because the prevalence of GADAb-positive non-insulin-dependent diabetes (SPIDDM/LADA syndrome) is high (around 10%) among various populations of patients with type 2 diabetes (7, 23). Patients in whom insulin can preserve β-cell function should easily achieve glycemic targets with less insulin and a lower frequency of injections and self-monitoring of blood glucose. Therefore, patients with preserved β-cell function have more stable glycemic control and a low occurrence of late diabetic complications (1, 2).

Explanations for the effectiveness of our intervention using insulin therapy in SPIDDM are based on the following. First, the suppression of β-cell activity by exogenous insulin will lead to β-cell rest with subsequent protection from damage by immunological and/or metabolic mechanisms (24, 25). Conversely, stimulating β-cells with a high glucose concentration and/or SU therapy potentially enhances the antigen expression of β-cells and their vulnerability to immunological attack (9, 24, 26). In addition, the metabolic effect of injected insulin might be associated with β-cell preservation because insulin reduces glucose toxicity to β-cells (27). Second, insulin *per se* protects against the apoptosis and necrosis of β-cells in type 1 diabetes (28). In type 2 diabetes after initiation of insulin or SU, the C-peptide response deteriorated in both modes of treatment (29). Exogenous insulin, which was an independent factor for a preferable outcome in the present study, will preserve endogenous insulin. Endogenous insulin will protect β-cells through autocrine and/or paracrine mechanisms in the islets. According to our study protocol, the half of the SU group patients with secondary failure in response to SU agents were switched to insulin, and patients also improved their glycemic control with a higher dose of insulin than that required by the Insulin group. This might explain the absence of a statistical difference in HbA_{1c} level between the two groups. The frequency of chemical hypoglycemia tended to be higher in the SU group than in the insulin group. This might be because a higher proportion of patients in the SU group rather than in the insulin group progressed to an insulin-dependent state and required more insulin. The increase in BMI might be explained as an insulin-associated weight gain (30) because the insulin dose was increased during the study in the insulin group, and SU agents were switched to insulin in half of the SU group patients. The significant increase of 2-h BG level in both groups might be due to a gain in body weight (BMI) with decreased insulin sensitivity and decreased insulin secretion during the study.

The reasons for the different outcomes between our study of SPIDDM and the Diabetes Prevention Trial-1 (DPT-1) of relatives of type 1 diabetic probands using insulin as a means of intervention (31, 32) remain speculative. The T cell response to β-cell antigens might be less aggressive in SPIDDM than in typical acute-onset type 1 diabetes in DPT-1 probands (5, 31–33). Exogenous insulin in SPIDDM patients will protect against weak T cell attack through immunological and metabolic mechanisms as noted above. The different results of the present and DPT-1 (31, 32) studies might be also explained by the genetic backgrounds of the patients. Only one diabetogenic histocompatibility leucocyte antigen (HLA) class II haplotype is related to SPIDDM (6, 34), whereas two diabetogenic HLA class II haplotypes and one class I haplotype are related to acute-onset type 1 diabetes (1, 6, 35). A single diabetogenic HLA haplotype might contribute to a less aggressive T cell attack against β-cells in SPIDDM. The genetic differences including HLA and other genetic factors between SPIDDM and LADA in various populations are not fully determined (6, 36). Therefore, the outcome of insulin intervention should differ in various populations according to HLA and/or other genetic factors.

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This trial has been submitted to clinicaltrials.gov. Study ID is NCT00232375.

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