Relationship Between Insulin-Dependent Diabetes Mellitus (IDDM) and Non–Insulin-Dependent Diabetes Mellitus: β-Cell Function, Islet Cell Antibody, and Haptoglobin in Parents of IDDM Patients

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To examine the relationship between non–insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM), we studied β-cell function, HLA type, and serologic markers of IDDM and NIDDM in the parents of IDDM patients. Fifty-two parents of 33 IDDM patients were examined in terms of islet-cell antibody (ICA) status, haptoglobin phenotype, HLA type, and insulin responses during an oral glucose tolerance test (OGTT). Twenty-seven parents were prospectively evaluated for up to 113 months. They were divided into the following three groups based on pattern of ICA positivity during the follow-up period: group 1, persistently positive ICA (n = 4); group 2, fluctuating ICA (n = 7); and group 3, persistently negative ICA (n = 16). Twenty-three percent (12 of 52) of the parents of IDDM patients had NIDDM, and 12% (six of 52) of the matched controls did. The prevalence of ICA in the parents (11 of 52, 21%) was greater than in normal controls (one of 112, $P < .01$). Diabetic parents tended to show a higher prevalence of ICA (six of 12, 50%) than nondiabetic parents (six of 40, 15%; $P = .06$). ICA-positive parents showed higher glucose levels and lower insulin responses than ICA-negative parents. Three of four parents in group 1 slowly progressed to an insulin-dependent state during 25 ± 3 months of follow-up evaluation. Parents in group 2 and group 3 did not show any changes in glucose levels or insulin responses during the study. Blood glucose levels at entry and during observation in groups 1 and 2 were higher than in group 3. Insulin responses in group 1 became lower than those in group 3 by the time the study was completed. Diabetic parents had higher frequencies of HLA-Bw54 and 1-2 haptoglobin phenotype. A high proportion of parents of IDDM patients have NIDDM. ICA-positive parents demonstrated low insulin responses. Our prospective study indicated that ICA is a marker of ongoing, slowly progressive β-cell destruction in parents of IDDM patients. It was also shown that ICA positivity in parents of IDDM patients can sometimes fluctuate. The high prevalence of NIDDM among parents of IDDM patients may be explained by persistent or fluctuating immunologic insults.

IT WAS RECENTLY FOUND that a high proportion of parents of insulin-dependent diabetes mellitus (IDDM) patients had non–insulin-dependent diabetes mellitus (NIDDM), suggesting that a relationship between IDDM and NIDDM[1] may lie in their common genetic background. In addition, the slowly progressive subtype of IDDM, in which β-cell dysfunction progresses through a non–insulin-dependent to an insulin-dependent state over several years, is prevalent in NIDDM.[2,3]

However, there is little information on serologic markers and genetic backgrounds of IDDM and NIDDM in the parents of IDDM patients,[4,5] especially in the Japanese. Furthermore, the natural history of β-cell dysfunction in parents of IDDM patients who have NIDDM is obscure. To clarify these unsettled questions, we evaluated the following parameters in parents of IDDM patients: (1) insulin response to oral glucose, (2) time course of β-cell function and positivity of islet-cell antibody (ICA), (3) prevalence of HLA types in parents of IDDM patients, and (4) their relationship with haptoglobin phenotype, which is a possible genetic marker of NIDDM.[6] We conducted a prospective study in some parents of IDDM patients.

SUBJECTS AND METHODS

Subjects

Fifty-two parents of 33 acute-onset IDDM patients (14 males and 19 females; mean ± SE age of onset, 20.1 ± 1.7 years) were recruited from 1980 through 1988 after consultation at the Diabetic Clinic of Toranomon Hospital. These parents were 21 fathers (aged 57.9 ± 1.8 years; range, 40 to 74) and 31 mothers (aged 54.9 ± 1.7; range, 36 to 77). No subjects have ever been checked for blood glucose levels. Fourteen parents did not participate in the study: seven fathers were dead, and five fathers and two mothers were unwilling to participate.

Controls for this population were enrolled in the Health Science Center for Medical Check of Toranomon Hospital during the same period. They visited this center for a general health examination. They were apparently healthy and had not received any medication for diabetes mellitus, hypertension, or hyperlipidemia. No subjects with abnormal liver or kidney function were included in the control group. They were matched with the recruited parents with respect to sex, age, height, and body weight. The mean age of the controls was 56.9 ± 1.2 years (range, 38 to 75). The mean height and body weight of controls were 158.4 ± 1.0 cm and 54.4 ± 1.2 kg, respectively, which were comparable with those of the parents (157.2 ± 1.1 cm and 53.4 ± 1.3 kg).

All parents and controls were residents of the Tokyo and Yokohama area and had generally equivalent social backgrounds.

Methods

All parents and controls underwent a 100-g oral glucose tolerance test (OGTT) at the outpatient clinic of Toranomon Hospital in the morning after a 12-hour overnight fast. They were on a diet containing greater than 250 g carbohydrate/d for 3 days before the

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OGTT. Following the American Diabetes Association recommendation,[7] information regarding diet, drugs, acute or chronic illnesses, etc., was elicited from the subjects not only when planning the test but also on the morning of the test. If the condition of a subject was not comparable to the standardization, the test was discontinued and repeated at another time.

Baseline samples were obtained for determination of capillary blood glucose, serum immunoreactive insulin (IRI), C-peptide immunoreactivity (CPR), ICA, HLA type, and haptoglobin phenotype. After oral ingestion of 100 g glucose, further blood samples for blood glucose, serum insulin, and CPR were obtained at 30, 60, 90, 120, and 180 minutes. Results of the OGTT were classified as a diabetic or nondiabetic pattern according to Joslin's standard guidelines.[8] The diagnostic values for diabetes are a 1-hour capillary whole glucose value of greater than 180 mg/dL and a 2-hour level greater than 160 mg/dL. Serum CPR was quantified as the integrated value of CPR levels at six sampling points (ΣCPR: normal value, 24 to 41 μg/mL). Serum samples obtained from the subjects were frozen at −80°C until analyzed for insulin, CPR, ICA, and haptoglobin phenotype. At the time of entry onto the trial, all parents were asked to visit our clinic at least every 6 months for ICA testing and an OGTT.

Blood glucose level was measured by the glucose oxidase method. Serum IRI level was measured by radioimmunoassay with kits from Dainabott Radioisotope Laboratory (Tokyo, Japan). Intraassay and interassay variances of IRI assays were 4% and 7%, respectively. All serum samples from each subject were grouped together and analyzed in the same IRI assay.

The detection method for ICA has been previously described.[9,10] Our laboratory participated in the second through fifth international workshops on standardization of ICA assay. The quality of our assay was class A: cutoff point, 5 Juvenile Diabetes Foundation (JDF) units; sensitivity, 90%; and specificity, 92%.[11] In our laboratory, 26 of 32 patients (81%) who became insulin-dependent within 6 months (mean ± SE, 0.12 ± 0.03 years) demonstrated positivity for ICA.

HLA typing was performed in 48 parents according to a standard microcytotoxicity test.[12] HLA typing of 203 normal subjects who were Japanese residents of the Tokyo and Yokohama area were used as normal controls.

Haptoglobin typing was performed according to the method reported by Roy et al[13] in 48 parents. Haptoglobin typing was also performed in 108 IDDM subjects, 156 NIDDM subjects, and 198 normal controls.

Statistics

The Mann-Whitney *U* test was used for unpaired samples. Wilcoxon's single-rank test was used for paired samples. Fisher's exact test was used to compare the incidence of glucose intolerance, ICA, HLA type, and haptoglobin phenotype among subjects. Results are expressed as the mean ± SE.

RESULTS

ICA and OGTT at Entry

Eleven of 52 parents of IDDM patients (21%) were positive for ICA at the time of entry. This prevalence was significantly higher than that of normal controls (one of 112, $P < .01$). The prevalence of ICA in the fathers and mothers was 14% (three of 21) and 26% (eight of 31), respectively.

Twenty-three percent (12 of 52) of the parents demonstrated a diabetic pattern to the OGTT, whereas 12% (six of 52) of the matched controls also had this pattern ($P = .097$). Parents with a diabetic pattern had a higher prevalence of ICA (50%, six of 12) than parents without a diabetic pattern (15%, six of 40; $P = .06$).

ICA-positive parents showed higher glucose levels than ICA-negative parents and their controls (Figs 1 and 2). ICA-positive parents tended to have lower insulin responses during the OGTT than ICA-negative parents (Fig 1). The response of serum IRI to OGTT was also quantified as the insulin to glucose ratio for the initial 30 minutes

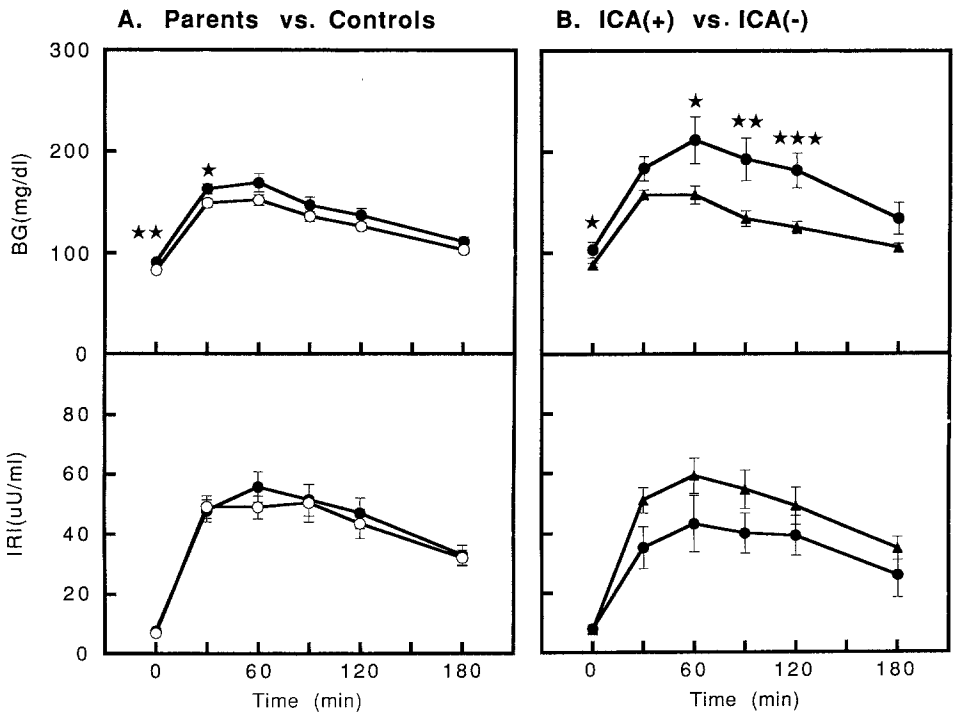

Fig 1. (A) Blood glucose (BG) and IRI responses to OGTT (mean ± SE) in parents of IDDM patients (n = 52, ●) and controls (n = 52, ○). ★$P < .05$ *v* controls; ★★$P < .01$ *v* controls. (B) BG and IRI responses to OGTT in ICA-positive parents (n = 11, ●) and ICA-negative parents (n = 41, ▲). ★$P < .05$ *v* ICA-negative; ★★$P < .01$ *v* ICA-negative; ★★★$P < .001$ *v* ICA-negative.

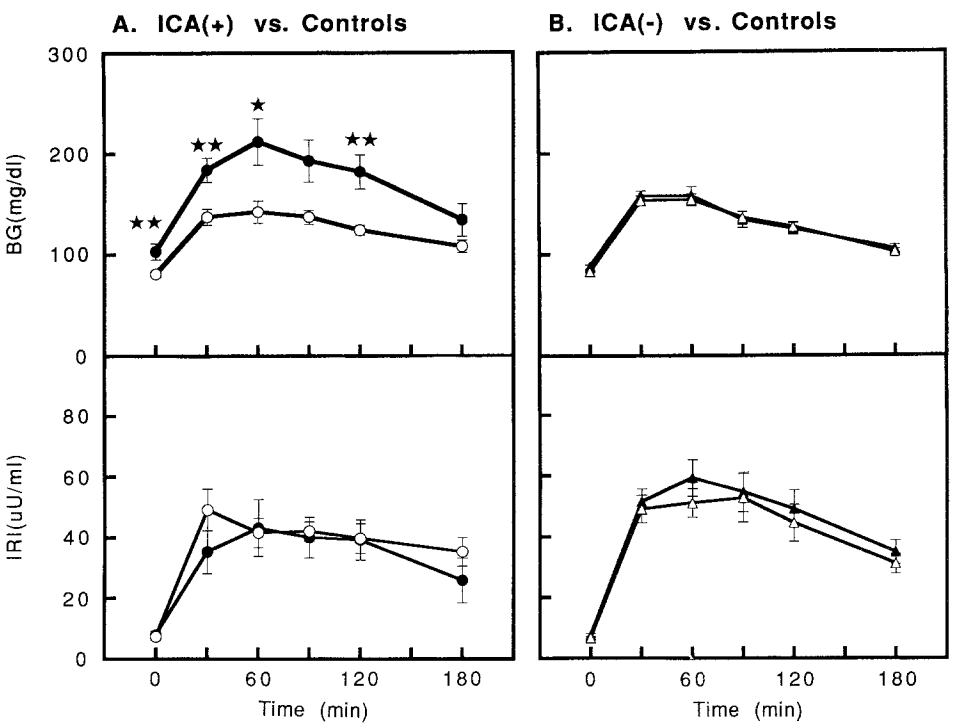

Fig 2. (A) Blood glucose (BG) and IRI responses to OGTT (mean ± SE) in ICA-positive parents (n = 11, ●) and their controls (n = 11, ○). ★P < .05 v controls; ★★P < .01 v controls. (B) BG and IRI responses to OGTT in ICA-negative parents (n = 41, ▲) and their controls (n = 41, △).

(ΔIRI/ΔBGF 30′). This value for ICA-positive parents (0.40 ± 0.11) was significantly less than for ICA-negative parents (0.68 ± 0.06, $P < .05$) and their controls (0.91 ± 0.19, $P < .05$). In contrast, there were no differences in glucose or IRI levels between ICA-negative parents and their controls (Fig 2).

Lower insulin responses were observed in ICA-positive diabetic parents as compared with ICA-negative diabetic parents (Fig 3). Blood glucose levels of ICA-positive diabetic parents were not different from those of ICA-negative diabetic parents.

None of the parents required sulfonylureas and/or insulin therapy at the time of entry.

Changes in ICA and CPR Responses to OGTT

To ascertain the relationship between ICA and glucose intolerance in the parents, we analyzed changes in ICA and CPR responses to OGTT. Twenty-seven of 52 parents (11 fathers and 16 mothers) participated in our follow-up study and were evaluated for up to 113 months (mean, 49 ± 6 months; range, 3 to 113), among whom eight parents (three fathers and five mothers) demonstrated a diabetic pattern at entry. The subjects were 10 ICA-positive and 17 ICA-negative parents at entry. Among the 10 ICA-positive parents, four (two fathers and two mothers) were persistently positive for ICA during the study (group 1, persistently ICA-positive group), whereas positivities of the remaining six parents fluctuated (group 2, fluctuating ICA positivity). Among 17 ICA-negative parents, one father demonstrated fluctuating ICA positivity (group 2), and the remaining 16 parents were persistently negative for ICA (group 3, persistently ICA-negative group).

To confirm and quantify the fluctuating ICA positivity,

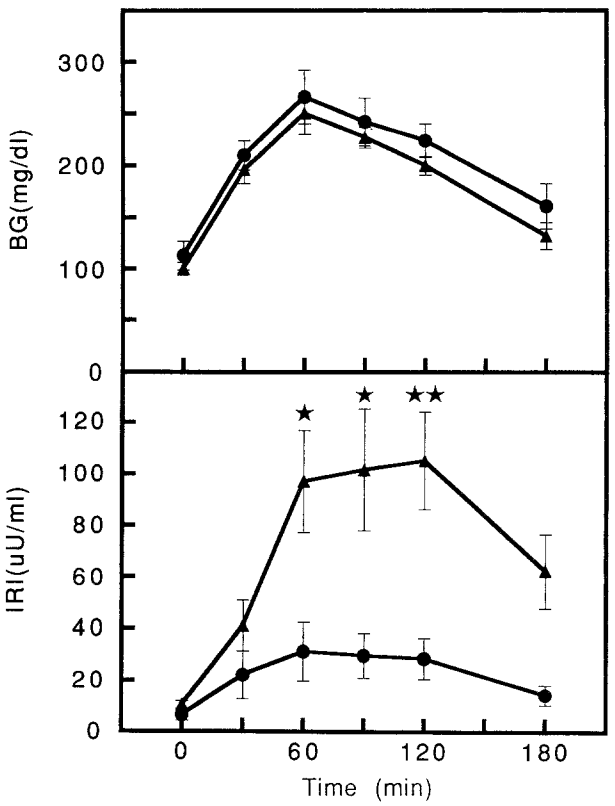

Fig 3. Blood glucose (BG) and IRI responses to OGTT (mean ± SE) in ICA-positive diabetic parents (n = 6, ●) and ICA-negative diabetic parents (n = 6, ▲). ★P < .05 v ICA-positive; ★★P < .01 v ICA-positive.

measurement of ICA titer was performed in a series of samples of the same patient in triplicate (Fig 4).

Parents in group 1 were younger than those in group 2, but sex, height, and body weight were comparable among groups 1, 2, and 3 (Table 1). Blood glucose levels at entry in groups 1 and 2 were significantly greater than those in group 3. CPR levels among groups 1, 2, and 3 were not significantly different. Three of four parents in group 1 required insulin because of elevated blood glucose levels 25 ± 3 months after entry and ultimately progressed to an insulin-dependent state with extremely diminished CPR responses (ΣCPR < 5 ng/mL). In group 2, glucose levels of one mother gradually increased, and insulin therapy was initiated 76 months later. Glucose levels and ΣCPR during the OGTT in group 2 did not show any change. In group 3, blood glucose levels and ΣCPR during the OGTT did not change overtime. At the end of follow-up evaluation, glucose levels in groups 1 and 2 were significantly greater than those in group 3, and ΣCPR in group 1 was significantly lower than in group 3 (Fig 5).

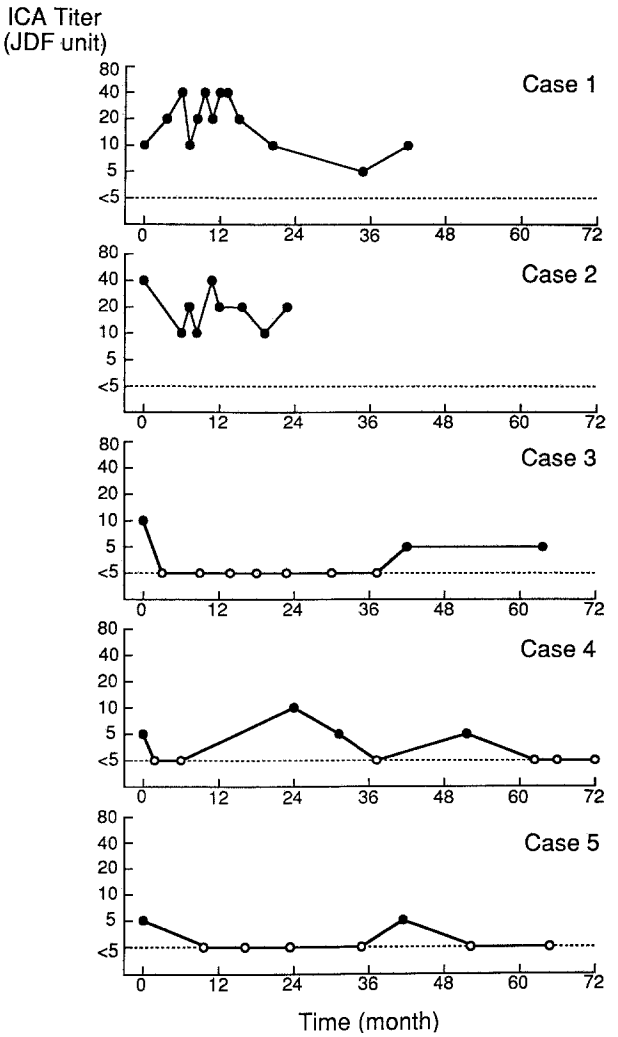

Fig 4. Longitudinal changes in ICA titer (JDF units) in 2 patients from group 1 (cases no. 1 and 2) and 3 patients from group 2 (cases no. 3, 4, and 5). ICA titers were measured in triplicate in a series of samples from the same patient; a concordant titer was demonstrated in each triplet.

Table 1. Demographic Characteristics of Study Subjects

Characteristic	Group 1 (n = 4)	Group 2 (n = 7)	Group 3 (n = 16)
Sex (M/F)	2/2	2/5	7/9
Age (yr)	53.3 ± 1.5	60.9 ± 1.3	51.4 ± 9.2
Body mass index (kg/m²)	20.4 ± 1.0*	21.7 ± 1.3*	21.6 ± 0.9
Follow-up period (mo)	26.5 ± 1.8	55 ± 8.1	51.4 ± 9.2

NOTE. Data are the mean ± SE.
*$P < .05$, group 1 *v* group 2.

HLA

Diabetic parents had a higher frequency of HLA-Bw54, which is positively associated with Japanese IDDM,[9] than nondiabetic parents and normal controls (Table 2). Frequencies of A24, DR2, and DR4 among diabetic parents were not different from those among nondiabetic parents or normal controls.

Initially ICA-positive parents did not have different frequencies of HLA type as compared with ICA-negative parents (Table 2). During the study, there were not statistically significant differences in the frequencies among groups 1, 2, and 3, although DR2 and DR4 tended to be highest in parents with fluctuating ICA (group 2). Frequencies of Bw54, DR2, and DR4 in groups 1, 2, and 3, respectively, were as follows: Bw54, one of four (25%), one of seven (14%), and three of 15 (25%); DR2, one of four (25%), four of six (67%), and five of 15 (33%); and DR4, one of four (25%), four of six (67%), and six of 15 (40%).

Haptoglobin Phenotype

Diabetic parents showed a significantly higher frequency of the 1-2 haptoglobin phenotype than nondiabetic parents, and this frequency also tended to be higher than that of normal controls (Table 3). There were no differences in the frequency of each haptoglobin phenotype among groups 1, 2, and 3.

DISCUSSION

The prevalences of ICA positivity and glucose intolerance in parents of IDDM patients in our study were much greater than previously reported in a white population.[4,14-23] In the Japanese population, the prevalence of ICA in NIDDM patients was 3.2%.[9] There are several possible reasons for this high prevalence of ICA. The greater sensitivity of the assay used in this study may be a factor. The cutoff point of the ICA assay in our study was 5 JDF units, and the sensitivity and specificity were both high.[9-11] In addition, the high prevalence of ICA-positive NIDDM in the parents may be related to genetic backgrounds in a Japanese population. The Japanese have a weak predisposition to IDDM because Japanese IDDM patients have only a single diabetogenic haplotype (HLA-DR4-DQA1*0301-DQB1*0401),[1,3] whereas in whites HLA-DR3-DQA1*0501-DQB1*0201 and DR4-DQA1*0301-DQB1*0302 heterozygotes (double diabetogenic haplotype) are common.[3,24-26] Late-onset IDDM is prevalent in the Japanese.[10,27,28] The

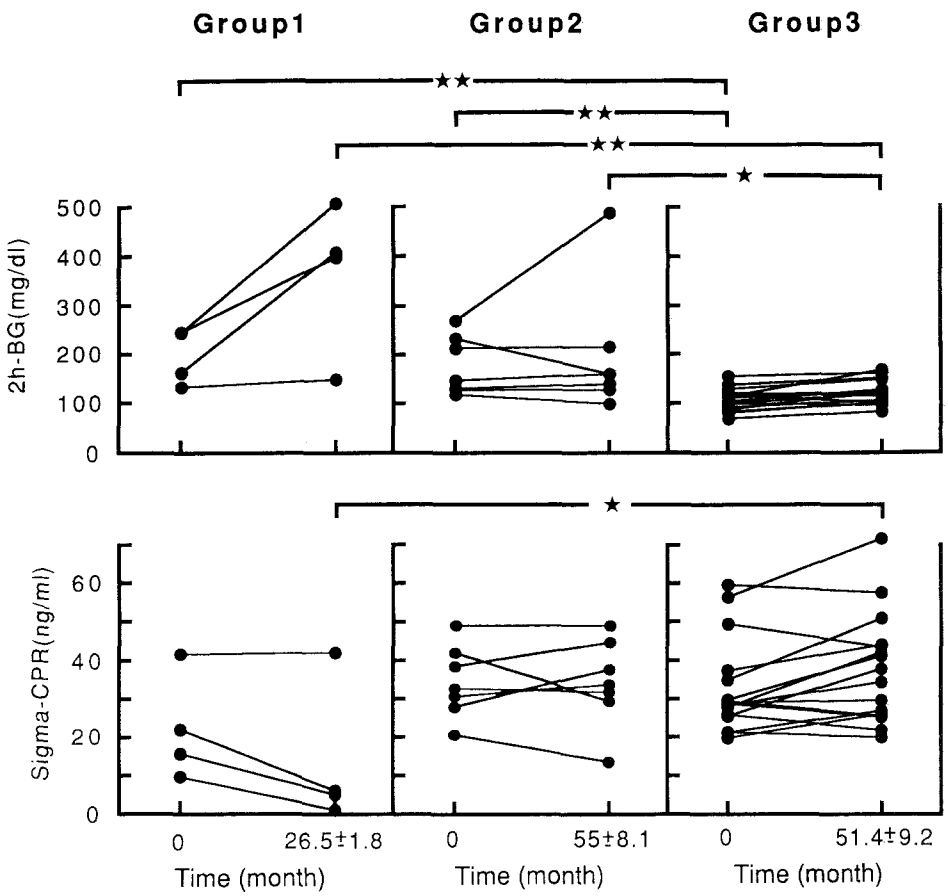

Fig 5. Alterations in blood glucose at 120 minutes (2h-BG) and integrated CPR responses (Sigma-CPR) during OGTT in groups 1, 2, and 3. ★P < .05; ★★P < .01.

pathologic process of β-cell failure sometimes progresses more slowly in the Japanese than in whites, and there is a higher prevalence of ICA-positive NIDDM in the Japanese.[2,29]

There is scant knowledge of the β-cell function of parents of IDDM probands,[4,5] especially in the Japanese. Significantly higher IRI responses to an OGTT were reported in ICA-positive parents as compared with ICA-negative parents.[4] In the present study, ICA-positive parents showed significantly lower IRI responses to an OGTT as compared with ICA-negative parents and controls (Fig 1). A mild degree of obesity of ICA-positive parents in the above-noted study may have contributed to the increased serum insulin levels.[4]

Three parents who were initially NIDDM had slowly progressive deterioration of β-cell function and became insulin-dependent. All of them were persistently positive for ICA, suggesting that ICA is a marker of ongoing, slowly progressive β-cell destruction, as described in cases of unrelated NIDDM.[10,30,31] Our recent study demonstrated the influence of a mitochondrial gene point mutation at nucleotide pair 3243 on slowly progressive β-cell failure.[32] Mitochondrial gene analysis in NIDDM parents may be required for further study.

During the study, some parents who were initially ICA-positive and had subsequent fluctuations of ICA positivity did not progress to an insulin-dependent stage and their β-cell function did not remarkably change. Lack of progression of subclinical β-cell dysfunction has often been observed in ICA-positive NIDDM patients.[10,20,33,34] Our data indicated that a portion of NIDDM parents with a β-cell autoimmune process may remain in a non–insulin-depen-

Table 2. HLA Frequencies in Parents According to ICA Positivity and Glucose Tolerance

	ICA				Glucose Tolerance					
	Positive		Negative		Diabetic		Nondiabetic		Control	
Antigen	No.	%	No.	%	No.	%	No.	%	No.	%
A24	8/11	67	22/37	61	10/12	83	20/36	56	114/203	56
Bw54	1/11	9	9/38	24	5/12	42*†	5/37	14	36/203	18
DR2	5/10	50	10/34	29	5/10	50	10/34	29	68/203	33
DR4	4/10	40	17/34	50	6/10	60	15/34	44	81/203	40

*P < .05 v nondiabetic.
†P = .055 v control.

Table 3. Frequencies of Haptoglobin Phenotypes According to ICA Positivity and Glucose Tolerance

	ICA				Glucose Tolerance					
	Positive (n = 11)		Negative (n = 37)		Diabetic (n = 12)		Nondiabetic (n = 36)		Control (n = 198)	
Phenotype	No.	%	No.	%	No.	%	No.	%	No.	%
1-1	1	9	2	5	1	8	2	6	17	9
1-2	4	36	10	27	7	58*†	7	19	63	32
2-2	6	55	25	68	4	33	27	75	118	60

*P < .05 v nondiabetic.
†P = .06 v control.

dent stage throughout life. Most of these parents had a fluctuating ICA status. In our study, the frequency of HLA-DR2 tended to be greater in parents with fluctuating ICA positivity. Our data suggest that HLA-DR2 in the parents may be associated with fluctuating ICA positivity and may also serve to protect against β-cell destruction in IDDM patients.[35] In addition, specific HLA loci were not associated with initial ICA positivity in parents of IDDM probands, as has been previously described.[4,21] This result may be explained by the transient nature of ICA, demonstrated in the present study and in other studies.[10,33]

The significance of haptoglobin phenotype in diabetes susceptibility is controversial.[6,36] In a Mexican-American population, a haptoglobin 1-1 homozygosity was associated with an increase in the prevalence of NIDDM.[6] In the present study, a greater frequency of 1-2 haptoglobin was observed in diabetic parents. In addition, these parents had a greater prevalence of HLA-Bw54, a diabetes-associated locus in a Japanese population. Further study is required to determine haptoglobin phenotypes in other ethnic groups to clarify the interrelationship between NIDDM and IDDM.

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