Increased Insulin Sensitivity and Decreased Insulin Secretion in Offspring of Insulin-Sensitive Type 2 Diabetic Patients

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To investigate the early defects of glucose metabolism in insulin-sensitive type 2 diabetes, we performed oral and frequently sampled intravenous glucose tolerance tests (OGTT and FSIGT) with minimal model analysis in 15 offspring of Japanese type 2 diabetics with normal insulin sensitivity (insulin resistance index of homeostasis model assessment [HOMA-R] < 2.0) and in 20 healthy control subjects without a family history of type 2 diabetes. The frequency of impaired glucose tolerance (IGT) was 40% (6 of 15) in the offspring and 0% (0 of 20) in the controls. Fasting plasma glucose (4.8 ± 0.1 *v* 4.6 ± 0.1 mmol/L, *P* = .18) and immunoreactive insulin ([IRI] 29.9 ± 2.5 *v* 28.3 ± 2.5 pmol/L, *P* = .64) were comparable between the offspring and the controls. The rate of glucose disappearance (K_G) was significantly lower in the offspring versus the control group (2.00 ± 0.22 *v* 2.60 ± 0.17 min^{-1}, *P* = .03). The insulin sensitivity index (Si) was significantly greater in the offspring versus the controls (2.68 ± 0.41 *v* 1.71 ± 0.17 × $10^{-4} \cdot min^{-1} \cdot$ pmol/L , *P* = .02). First-phase insulin secretion (FPI) to intravenous glucose was significantly lower in the offspring versus the control group (886 ± 110 *v* 2,296 ± 267 min · pmol/L, *P* < .01). Glucose effectiveness (S_G) was comparable between the offspring and control groups. The disposition index (Si × FPI) was significantly lower in the offspring versus the controls (2,106 ± 256 *v* 3,652 ± 490 × 10^{-4}, *P* = .02). When the offspring were subdivided into 2 groups by glucose tolerance status, both normal glucose tolerance (NGT) offspring and IGT offspring showed a significant decrease in FPI and increase in Si. Thus, although the offspring of insulin-sensitive type 2 diabetics had increased insulin sensitivity, the impairment in insulin secretion was more dominant. Our results suggest that the early metabolic abnormality in insulin-sensitive type 2 diabetes is an insulin secretory dysfunction despite increased insulin sensitivity.
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BOTH INSULIN SECRETORY dysfunction and insulin resistance are involved in the pathogenesis of type 2 diabetes mellitus.[1-4] However, which of these 2 abnormalities is the primary cause of type 2 diabetes is still controversial.[5-7] In Pima Indians and Caucasians, insulin resistance is believed to be the primary defect in type 2 diabetes, because in the prediabetic state, subjects such as patients with impaired glucose tolerance (IGT) or the offspring of type 2 diabetics characteristically have insulin resistance or compensatory hyperinsulinemia.[8-10] In some ethnic groups, especially Japanese and African-Americans, the presence of insulin-sensitive type 2 diabetes has been recognized.[11,12]

We previously reported that about 50% of non-obese Japanese type 2 diabetic patients were insulin-sensitive based on the insulin resistance index of the homeostasis model assessment (HOMA-R).[13] However, the metabolic features of the prediabetic state in insulin-sensitive type 2 diabetics have not yet been studied. Therefore, we investigated insulin secretion and insulin sensitivity in the offspring of non-obese Japanese patients with insulin-sensitive type 2 diabetes using Bergman's minimal model analysis.

SUBJECTS AND METHODS

Insulin-Sensitive Type 2 Diabetic Patients

Patients with non-obese (body mass index [BMI] < 25 kg/m^2) insulin-sensitive type 2 diabetes were selected among those attending the outpatient clinic at Sasebo Chuo Hospital or Nagasaki University Hospital. Type 2 diabetes was diagnosed according to the criteria of the American Diabetes Association.[14] To exclude type 1 diabetics, islet-cell antibody (ICA) and anti–glutamic acid decarboxylase (GAD) antibody[15,16] levels were measured in each patient. Insulin sensitivity in diabetic patients was measured by HOMA using fasting glucose and immunoreactive insulin (IRI) levels.[17] According to our previous report,[13] a HOMA-R value less than 2.0 defined an insulin-sensitive state in this study. Patients whose onset age of diabetes was earlier than 25 years were excluded from the study. Patients with diabetes due to a mutation in mitochondrial DNA were also excluded from the study.[18] Eleven insulin-sensitive type 2 diabetic patients and their 15 offspring participated in this study. We also included 20 control subjects. The clinical characteristics of the insulin-sensitive type 2 diabetic patients were as follows: 7 men and 4 women; mean age, 60.2 ± 2.4 years; mean BMI, 21.6 ± 0.6 kg/m^2; and mean HOMA-R, 1.73 ± 0.08. Three patients were treated with diet alone, 5 patients with a sulfonylurea, and 3 patients with insulin. The study protocol was approved by the Ethics Committee of Sasebo Chuo Hospital and Nagasaki University Hospital, and a signed consent form was obtained from each subject.

Offspring and Control Groups

The offspring of type 2 diabetics were healthy and using no medications. In addition, they were negative for ICA and anti-GAD antibody and showed no mutation in mitochondrial DNA. The control subjects were not using any medications and had no family history of type 2 diabetes. The gender, age, height, body weight, and BMI of the offspring and control subjects were comparable (Table 1). All study subjects were placed on a weight-maintaining diet (30 to 35 kcal/ideal body weight). None of the subjects performed heavy exercise for at least 1 week before the test.

Study Protocol

Each subject underwent a 75-g oral glucose tolerance test and an insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT). The insulin-modified FSIGT was performed as previously described by our laboratory.[19,20] Briefly, baseline samples were obtained at −20, −10, and −3 minutes prior to intravenous glucose administra-

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Table 1. Clinical Characteristics of the Offspring of Insulin-Sensitive Type 2 Diabetics and the Control Subjects

Characteristic	Control	Offspring
No. of subjects (male/female)	20 (11/9)	15 (7/8)
Age (yr)	29.2 ± 1.3	27.2 ± 1.0
Height (cm)	163.1 ± 0.02	164.8 ± 0.02
Body weight (kg)	57.6 ± 1.5	56.2 ± 2.4
BMI (kg/m^2)	21.6 ± 0.3	20.6 ± 0.6
NGT (n)	20	9
IGT (n)	0	6

NOTE. Data are the mean ± SE.

tion at a dose of 300 mg/kg body weight over 1 minute, and 27 subsequent samples were obtained. Insulin (Humulin R; Eli Lilly, Kobe, Japan) at a dose of 20 mU/kg body weight was infused from 20 to 25 minutes after administration of glucose.

The plasma glucose level was measured by a glucose oxidase method (Kyoto-Daiichi Kagaku, Kyoto, Japan). The IRI level was measured by a commercial radioimmunoassay kit (Shionogi, Osaka, Japan).

Data Analysis

The rate of glucose disappearance (KG) was calculated as the slope of the least-square regression line relating the natural logarithm of glucose concentration to time, using 5 samples drawn between 10 and 19 minutes. The insulin sensitivity index (Si) and glucose effectiveness (SG) were estimated by Bergman's minimal model analysis.[21,22] The basal insulin effect (BIE) represented the product of basal insulin and Si (BIE = basal insulin × Si). Glucose effectiveness at zero insulin (GEZI) is the difference between SG and BIE. First-phase insulin (FPI) secretion in the FSIGT was expressed as the integrated area under the insulin curve above the basal level between 0 and 10 minutes. In this study, we also calculated the disposition index, representing the product of Si × FPI, which is constant in healthy individuals.[23]

Statistical Analysis

Statistical analysis was performed with the 2-tailed Student's *t* test. Data are expressed as the mean ± SE. Differences were considered statistically significant at a *P* level less than .05.

RESULTS

OGTT (75 g)

All control subjects showed normal glucose tolerance (NGT) on the 75-g OGTT. Among the offspring, 9 showed NGT and 6 showed IGT. The mean plasma glucose and serum IRI during the 75-g OGTT are depicted in Fig 1. Plasma glucose concentrations at 30, 60, and 90 minutes after glucose ingestion were significantly higher in the offspring versus the control group. The area under the glucose curve ($AUC_{glucose}$) during the OGTT in the offspring was significantly greater versus the control group (935.3 ± 58.6 and 755.8 ± 25.0 mmol · min/L, $P = .01$, respectively). Serum IRI levels at 30 and 60 minutes after glucose ingestion tended to be lower while those at 90 and 120 minutes tended to be higher in the offspring versus the control group, albeit insignificantly (Fig 1B). The $AUC_{insulin}$ during the OGTT was comparable in the offspring versus the controls (25,814 ± 2,766 and 26,554 ± 2,351 pmol · min/L, $P = .84$, respectively).

FSIGT and Minimal Model Analysis

The mean plasma glucose and serum IRI during the insulin-modified FSIGT are shown in Fig 2, and the results of minimal model analysis are shown in Table 2. Fasting plasma glucose and serum IRI levels were comparable among the offspring and control groups ($P = .18$ and .64, respectively). KG was significantly slower in the offspring versus the controls ($P = .03$). Si was significantly greater in the offspring versus controls ($P = .02$), suggesting increased insulin sensitivity in the offspring of insulin-sensitive type 2 diabetics. SG, GEZI, and BIE were not significantly different between offspring and control groups ($P = .84$, .14, and .07, respectively). The FPI to intravenous glucose was significantly lower in the offspring versus the controls ($P < .01$), suggesting impaired insulin secretion. The disposition index was significantly lower in the offspring versus controls ($P = .02$). Considered together, these results suggest that although the offspring of insulin-sensitive type 2 diabetics had increased insulin sensitivity, the impairment of insulin secretion is the dominant pathology.

Subanalysis According to the Glucose Tolerance State

We analyzed the results separately by the glucose tolerance state of the offspring (Table 2). Fasting glucose and insulin were comparable among NGT and IGT offspring. NGT offspring showed a significantly lower FPI ($P < .01$) and a tendency for higher Si ($P = .057$) compared with the controls. However, NGT offspring showed similar values for KG, SG, GEZI, and the disposition index compared with the controls. IGT offspring

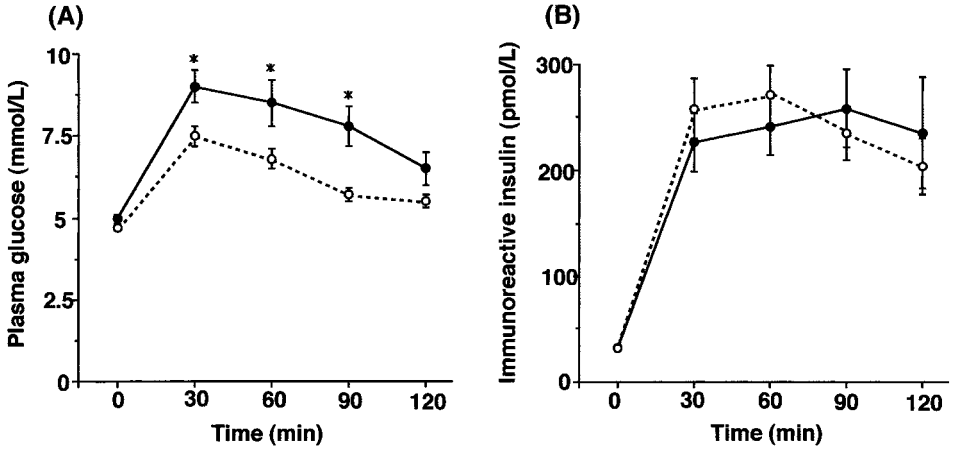

Fig 1. Plasma glucose (A) and immunoreactive insulin (B) measured during a 75-g OGTT in the offspring of insulin-sensitive type 2 diabetics (●) and in controls (○). *$P < .05$ *v* control.

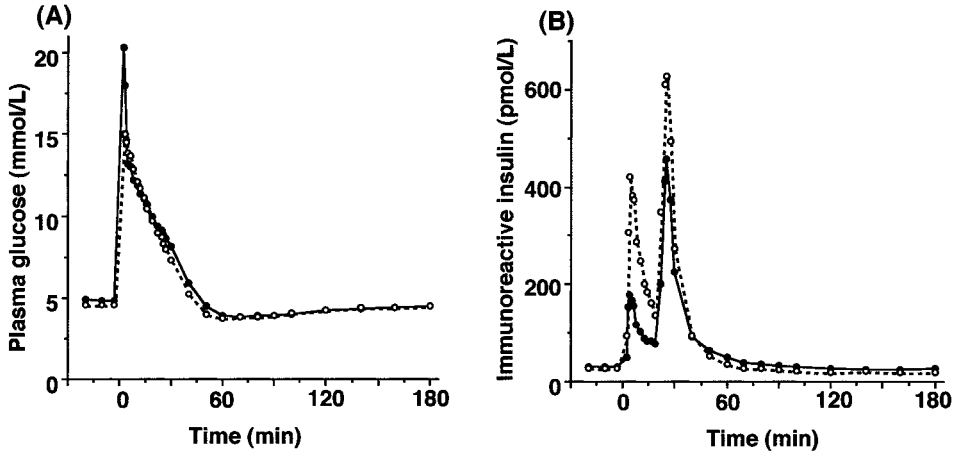

Fig 2. Mean plasma glucose (A) and immunoreactive insulin (B) measured during the modified FSIGT in the offspring of insulin-sensitive type 2 diabetics (●) and in controls (○).

showed a significantly lower FPI ($P < .01$) and higher Si ($P < .05$) compared with the controls. The KG ($P < .01$) and disposition index ($P < .05$) were significantly decreased in IGT offspring. GEZI tended to be lower in IGT offspring versus controls, albeit insignificantly ($P = .063$).

DISCUSSION

The presence of insulin-sensitive type 2 diabetes has been reported in some ethnic groups such as African-American, lean Scandinavian, and Japanese.[11,12,24] The predominant cause of diabetes in such patients may be an insulin secretory dysfunction rather than insulin resistance.

In the present study, we studied the offspring of non-obese insulin-sensitive Japanese type 2 diabetic patients and found the following results: (1) the KG was significantly slower in the offspring than in the controls, (2) FPI was significantly reduced in the offspring by 61% compared with the controls, (3) insulin sensitivity was increased in the offspring compared with controls, and (4) increased insulin sensitivity could not compensate for impaired insulin secretion in the offspring because the disposition index in these subjects was significantly lower versus the control group. Our results suggest that the clinical characteristics of the prediabetic state in insulin-sensitive type 2 diabetes include an increased insulin sensitivity and a marked insulin secretory dysfunction. Hence, the primary cause of disease in insulin-sensitive type 2 diabetes is likely an insulin secretory dysfunction. We hypothesize that insulin-deficient offspring presently do not develop diabetes because of their increased insulin sensitivity, but when their insulin sensitivity decreases slightly through aging, sedentary life-style, or body fat accumulation, they may easily develop diabetes.

In our previous cross-sectional study, a worsening of glucose tolerance in Japanese subjects was closely related to an impairment in early-phase insulin secretion.[13] In a longitudinal study of Japanese-Americans, Chen et al[25] reported that an impairment of early-phase insulin secretion was an important and significant predictor of future type 2 diabetes. Furthermore, we reported that Japanese women with former gestational diabetes, which is another prediabetic state, showed insulin secretory dysfunction.[26] These results suggest that the primary cause of diabetes in Japanese patients may be a pancreatic β-cell dysfunction, and a decrease in insulin sensitivity may trigger the development of diabetes.

Using the minimal model approach, Doi et al[27] reported that the offspring of Japanese type 2 diabetics had decreased FPI and SG but normal Si. In contrast, Osei et al[28] reported that the offspring of type 2 diabetics had normal SG but decreased Si. Furthermore, Henriksen et al[29] studied Danish offspring of type 2 diabetics and reported increased SG and decreased Si. These results, including ours, suggest that the pathogenesis of type 2

Table 2. Results of the FSIGT and Minimal Model Analysis

Parameter	Control (n = 20)	All Offspring (n = 15)	NGT Offspring (n = 9)	IGT Offspring (n = 6)
Fasting glucose (mmol/L)	4.6 ± 0.1	4.8 ± 0.1	4.7 ± 0.1	5.1 ± 0.3
Fasting insulin (pmol/L)	28.3 ± 2.5	29.9 ± 2.5	30.4 ± 3.0	29.3 ± 4.6
KG (min^{-1})	2.60 ± 0.17	2.00 ± 0.22*	2.46 ± 0.24	1.31 ± 0.18†
Si ($\times 10^{-4} \cdot min^{-1} \cdot pmol/L$)	1.71 ± 0.17	2.68 ± 0.41*	2.43 ± 0.38	3.06 ± 0.89*
SG ($\times 10^{-2} \cdot min^{-1}$)	2.20 ± 0.23	2.13 ± 0.23	2.33 ± 0.33	1.83 ± 0.28
GEZI ($\times 10^{-2} \cdot min^{-1}$)	1.71 ± 0.19	1.33 ± 0.15	1.56 ± 0.17	1.00 ± 0.23
BIE ($\times 10^{-2} \cdot min^{-1}$)	0.49 ± 0.08	0.80 ± 0.16	0.77 ± 0.20	0.83 ± 0.28
FPI (min · pmol/L)	2,296 ± 267	886 ± 110†	1,060 ± 124†	624 ± 157†
Disposition index ($\times 10^{-4}$)	3,652 ± 490	2,106 ± 256*	2,503 ± 336	1,511 ± 266*

NOTE. Data are the mean ± SE.

*$P < .05$ *v* control.

†$P < .01$ *v* control.

Abbreviations: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; KG, rate of glucose disappearance; Si, insulin sensitivity index; SG, glucose effectiveness; GEZI, glucose effectiveness at zero insulin; BIE, basal insulin effect; FPI, first-phase insulin; disposition index, Si × FPI.

diabetes is quite heterogeneous. Recently, Araujo et al[30] reported that a decrease in K_G was associated with a decrease in S_G (or GEZI) and a decrease in FPI in the offspring of type 2 diabetics. Similarly, in our study, IGT offspring showed a significant decrease in K_G and also showed a tendency for a decrease in GEZI and FPI. Therefore, we speculate that S_G (or GEZI) in the offspring may decrease when their K_G and FPI are significantly deteriorated.

The reason for the difference between our results and others[27-29] is not clear at this stage. One possible reason may be the difference in the characteristics of the proband diabetic patients studied. Our patients were non-obese (BMI < 25 kg/m^2) and had normal insulin sensitivity (HOMA < 2.0), but the characteristics of type 2 diabetics in the other studies were not clear. In this regard, Vauhkonen et al[31] reported that insulin secretory dysfunction and insulin resistance were separately inherited in the offspring of type 2 diabetics. When studying metabolic features of the offspring of type 2 diabetics, the phenotypic characterization of the patients has to be established.

Our study has some limitations. First, a clinical study like ours cannot identify the true cause of disease. Recently, certain specific abnormalities that can induce insulin secretory dysfunction have been identified. Although we screened for anti-GAD antibody, ICA, and mitochondrial DNA mutation, other abnormalities such as mutations in maturity-onset diabetes of the young (MODY) genes were not screened.[32] However, it is reported that MODY genes are not common in Japanese late-onset type 2 diabetes.[33] Furthermore, we excluded proband patients whose onset age of diabetes was earlier than 25 years in this study. Hence, the cause of diabetes in our selected patients is unlikely to be mutations in MODY genes. Second, the sample number was small in this study. To confirm our hypothesis, another study of a larger population sample is necessary. Third, our study design was cross-sectional rather than longitudinal, and hence it does not establish that the offspring will actually develop type 2 diabetes.

In conclusion, we have shown in this study that the clinical characteristics of the prediabetic state in insulin-sensitive and lean Japanese type 2 diabetes include an increased insulin sensitivity and a marked insulin secretory dysfunction. A slight decrease in insulin sensitivity may trigger the development of diabetes in these subjects. It seems that the maintenance of increased insulin sensitivity is an effective strategy to prevent diabetes in such subjects.

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