Pathogenic Factors of Glucose Intolerance in Obese Japanese Adolescents With Type 2 Diabetes

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We attempted to identify the pathogenic factors involved in the progression to type 2 diabetes in obese Japanese adolescents. Subjects included 18 nondiabetic obese adolescents, 12 obese adolescents with type 2 diabetes on diet therapy, 10 obese adolescents with type 2 diabetes manifesting ketosis at onset or with a history of treatment with hypoglycemic agents, and 26 non-obese adolescent control subjects. The first-phase insulin response (FPIR), glucose disappearance constant (K_g), glucose effectiveness (S_g), and insulin sensitivity (S_I) were obtained using an insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT) and a minimal model analysis. The disposition index (DI, by FPIR × S_I) was determined to assess any endogenous insulin effect. The results showed that K_g was decreased significantly ($P = .0006$) with the progression to severe diabetes in the obese groups. Although S_I and S_g did not differ significantly among the 3 obese groups, both parameters were significantly lower in each obese group versus the non-obese controls. As a result of the significant decrease in FPIR ($P < .0001$), the DI decreased ($P = .0006$) with the progression to severe diabetes in the obese groups. In conclusion, an early manifestation of type 2 diabetes with occasional ketosis at onset may result from β-cell dysfunction to glucose stimulation. This finding is demonstrated by the relatively low FPIR to decreased S_I in obese Japanese adolescents, as well as the low S_g as a synergic role in glucose intolerance. The present findings from a Japanese population for pathogenic factors aside from obesity may help us to gain a better understanding of the progression to adolescent, early-onset, obese type 2 diabetes and its severity.

ONLY A SMALL NUMBER of studies have investigated adolescent-onset type 2 diabetes.[1-4] The prevalence of adolescent obesity is increasing in Japan[1] and the United States,[2,3] and the incidence of obese type 2 diabetes (non–insulin-dependent diabetes mellitus [NIDDM]) in Japanese adolescents is roughly equivalent to the US rate (Greater Cincinnati, ~6/100,000 population/yr in Japan *v* 7.2/100,000 population/yr in the Cincinnati sample).[1,2]

In terms of genetic influence, the younger a person is at diabetic onset, the higher the percentage of diabetes tends to be in his or her family history, as found in patients with maturity-onset diabetes of the young. Thus, we must consider precipitating factors other than obesity when we apply the "thrifty genes" hypothesis[5] to adolescent-onset diabetes.

On the other hand, some similarities have been shown to exist in the clinical characteristics of obese diabetes mellitus among both Japanese adolescents and an African-American population, including a relatively young age at onset and occasional ketosis at onset.[6,7] Although the subjects in their study were middle-aged, Osei et al[7] reported a concomitant decrease in the first-phase insulin response (FPIR) with the progression to severe diabetes in African-Americans, despite a decrease in insulin sensitivity (S_I) as demonstrated by the frequently sampled intravenous glucose tolerance test (FSIGT) using minimal model analysis. There have been a number of reports in Japanese populations suggesting a racial predisposition for low glucose effectiveness (S_g), as demonstrated in subjects with non-obese type 2 diabetes,[8] subjects with impaired glucose tolerance (IGT),[9,10] and nondiabetic offspring of patients with type 2 diabetes.[11] The offspring of patients with type 2 diabetes also showed a relatively reduced FPIR to S_I in comparison to subjects without type 2 diabetes.[11]

However, none of these studies characterized the actual determinants or the contribution of various components to glucose homeostasis in obese adolescent type 2 diabetics with varying degrees of glucose intolerance. Therefore, we attempted to identify any pathogenic factors aside from obesity that are involved in the progression to type 2 diabetes in Japanese adolescents.

SUBJECTS AND METHODS

Subjects

An insulin-modified FSIGT was used to assess 18 nondiabetic obese adolescents (group A), 12 obese adolescents with type 2 diabetes on diet therapy (group B), and 10 obese adolescents with type 2 diabetes manifesting ketosis at onset or with a history of treatment with hypoglycemic agents (group C). Group C had a history of more severe chronic hyperglycemia as detected by hemoglobin A_{1c} (HbA_{1c}) greater than 9% compared with group B. Seven group C patients (70%) were initially treated with insulin due to ketosis or ketoacidosis detected at onset. The remaining 3 patients had a history of treatment with hypoglycemic agents other than insulin, due to the above-mentioned persistent hyperglycemia. Although all of them required intensive treatment with insulin or other hypoglycemic agents in each hyperglycemic episode, they attained near-normoglycemia within 1 month. Six of them were treated with hypoglycemic agents only at 1 episode. Although 4 patients, including 2 with ketosis at onset, continued to be treated with minimal doses of hypoglycemic agents for strict glycemic

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control, all group C patients were actually free of hypoglycemic medication without hyperglycemic deterioration at least 1 month before this study. The control subjects were 26 healthy non-obese adolescents. No subjects in this study had islet cell antibodies or an antibody to glutamic acid decarboxylase. The demographic and basal metabolic data are listed in Table 1, including the history of ketosis or ketoacidosis at onset and the percentage of diabetics in first-degree relatives in each group. Informed written consent was obtained from each subject and his or her parents after a thorough explanation of the risks involved in the study. The study was approved by the Medical Ethics Committee of Yamanashi Medical University.

The obesity index (OI) was determined by calculating the percentage of standard body weight for Japanese adolescents according to height, sex, and age (Growth Checker, Sumitomo Pharmaceutical, Osaka, Japan). The body mass index (BMI) was calculated as the weight (kilograms) divided by the square of the height (meters). All group B and C subjects had a BMI greater than 26 kg/m^2 and an OI greater than 130% at diabetes onset, indicating obesity.[12]

Study Protocol

All subjects were free of any dietary restrictions for a minimum of 3 days before the start of the study. The patients fasted overnight on the day before the test. The fasting plasma glucose (FPG) was confirmed to less than 126 mg/dL (7.0 mmol/L) by a bedside monitor at baseline sampling. This was used to eliminate all subjects with a diabetic level of FPG.[13] Body weight and height were measured with the subjects wearing a light gown without shoes.

With the subjects in a supine position, 2 venous catheters were inserted into different forearm veins. The 2 routes were kept patent with 0.9% normal saline infusion. One intravenous line was used for blood sampling, while the other was used to administer intravenous glucose and exogenous insulin. After a 15-minute rest, more than 2 samples were taken as the basal fasting value for plasma glucose and insulin. The loading intravenous dose of glucose was 0.3 g/kg standard body weight infused over 2 minutes. Regular insulin at 0.02 to 0.04 U/kg standard body weight for Japanese adolescents based on height, sex, and age (Novolin R; Novo Nordisk, Tokyo, Japan) was infused over the 5-minute period from 20 to 25 minutes of the test. In the non-obese control subjects and simple-obesity patients, regular insulin 0.02 U/kg was infused. Regular insulin 0.03 U/kg was infused in group B, and regular insulin 0.04 U/kg was infused in group C. The larger dose of insulin was used in the diabetic groups to avoid any calculation error in S_I due to a low FPIR, which results in a poor reduction in plasma glucose and was suspected in diabetic patients, based on our preliminary study. Blood samples were obtained at frequent intervals at 2, 6, 10, 14, 19, 26, 28, 30, 36, 40, 50, 80, 120, and 180 minutes following the glucose infusion. This was based on our reduced-sampling FSIGT protocol, modified based on previous reports.[14-19]

Laboratory Methods

The serum insulin concentration was measured using an enzyme immunoassay (AIA 1200; Toso, Tokyo, Japan). The coefficient of variation for the insulin assay was 7.9% at 91.2 pmol/L and 7.1% at 730 pmol/L. The plasma glucose level was measured using a glucose oxidase method (model 7250; Hitachi, Tokyo, Japan). The measurement error of glucose was assumed to be due to the "white" Gaussian noise of 0 means and a coefficient of variation of 1.5%. HbA_{1c} was determined by high-performance liquid chromatography; The upper-limit reference value of HbA_{1c} was 5.8%. Urine C-peptide was determined by radioimmunoassay (Shionogi, Osaka, Japan).

Data Analysis

The glucose disappearance constant (K_g) was calculated as the slope of the least-square regression line relating the natural logarithm of the glucose concentration to time from 3 samples drawn between 10 and 19 minutes.[8] FPIR was determined as the area under the insulin curve during the first 10 minutes, using the trapezoidal method.[8] S_I and S_g were estimated using the minimal model approach.[20,21] The basal insulin effect (BIE) was calculated as the product of basal insulin (Ib) and S_I as follows, assuming that the effect of insulin from 0 to basal is linear: BIE = Ib × S_I.[9,10] Glucose effectiveness at zero insulin (GEZI) is the difference between S_g and BIE, GEZI = S_g − (Ib × S_I) = S_g − BIE.[9,10]

The minimal model program was written in Pascal as described previously.[20] The values from 0 to 8 minutes were 0-weighted as suggested by Pacini and Bergman.[21] Since Kahn et al[22] suggested a hyperbolic relationship between S_I and FPIR to compensate for any insulin resistance, the authors calculated the disposition index (DI) as the product of S_I and FPIR. They modeled the relationship on an assessment of the accumulated data for the DI including this study and previous reports.[9,10,14] The curvilinear relationship between S_I and FPIR was statistically significant (R^2 = .333, N = 70, P < .0001), ie, S_I × FPIR = constant (0.3959 ± 0.2389, mean ± SD).

Table 1. Demographic and Basal Metabolic Data for the Subjects (mean ± SE)

Variable	(A) Simple Obesity	(B) Obese Type 2 Diabetes on Diet Only	(C) Obese Type 2 Diabetes With Hypo Agent	*P* A v B	*P* A v C	*P* B v C	*P* ANOVA	Non-obese Controls
No. of subjects	18	12	10	—	—	—	—	26
Gender (male/female)	15/3	7/5	4/6	—	—	—	—	17/9
Age (yr)	14.3 ± 0.7	14.0 ± 0.5	16.0 ± 1.4*	NS	NS	NS	NS	13.5 ± 0.4
Duration (mo)	—	15.9 ± 4.5	35.3 ± 15.9	—	—	NS	—	—
Ketosis at onset (%)	—	—	70.0	—	—	—	—	—
Diabetes in first-degree relatives (%)	5.5	41.6	60.0	—	—	—	—	—
BMI (kg/m^2)	29.5 ± 0.7†	27.9 ± 1.7†	26.0 ± 1.3†	NS	.0133	NS	NS	18.2 ± 0.4
OI (%)	149.8 ± 4.5†	139.7 ± 7.6†	129.7 ± 5.6†	NS	.0048	NS	NS	94.9 ± 1.8
FPG (mg/dL)	90.5 ± 1.9	101.4 ± 4.4†	107.8 ± 3.7†	.0051	<.0001	NS	.0014	89.0 ± 1.4
Ib (pmol/L)	112.9 ± 9.9†	140.3 ± 27.5†	80.6 ± 13.9	NS	NS	.0091	NS	61.1 ± 5.4
HbA_{1c} (%)	5.4 ± 0.1	5.7 ± 0.3†	6.6 ± 0.4†	NS	.0003	.017	.0158	5.1 ± 0.1
CPR (μg/d)‡	—	96.7 ± 3.5	73.9 ± 13.2	—	—	NS	—	—

Abbreviations: NS, not significant; —, not evaluated; Hypo, hypoglycemic; CPR, C-peptide.

*P < .05 *v* control.

†P < .01 *v* control.

‡Reference range, 32-122 μg/d.

Statistics

Data are presented as the mean ± SE unless otherwise indicated. Analyses of parameters among the 3 groups were first performed using ANOVA for multiple comparisons; differences between each group were then evaluated by Fisher's partial least-square difference post hoc test. The relationship between any 2 variables was calculated by simple regression. Statistical significance was determined by a P level less than .05. Stepwise multiple regression analyses were applied to K_g as a dependent variable explained by the independent variables of the other 11 clinical and laboratory parameters, including the BMI, OI, FPG, Ib, FPIR, S_g, S_I, DI, BIE, GEZI, and HbA_{1c}.

RESULTS

Data for the parameters of the FSIGT with minimal model analysis are shown in Fig 1 and Table 2. There was a statistically significant difference ($P = .0006$) in K_g among the 3 obese groups, although the difference between groups B and C did not reach statistical significance. There were also significant differences in K_g between the non-obese controls and the obese groups (each $P < .005$; Fig 1a) and a statistically significant difference ($P < .0001$) in FPIR among the obese groups. Group A showed a significantly (each $P < .005$) higher FPIR than the other 3 groups (Fig 1b). S_I was decreased significantly more in the 3 obese groups versus the non-obese controls ($P < .05$), but did not differ significantly among the obese groups (Fig 1c). S_g was also decreased significantly more in the obese groups versus the non-obese controls ($P < .005$), but also did not differ significantly among the 3 obese groups (Fig 1d). There was a statistically significant difference in the DI ($P = .0006$) among

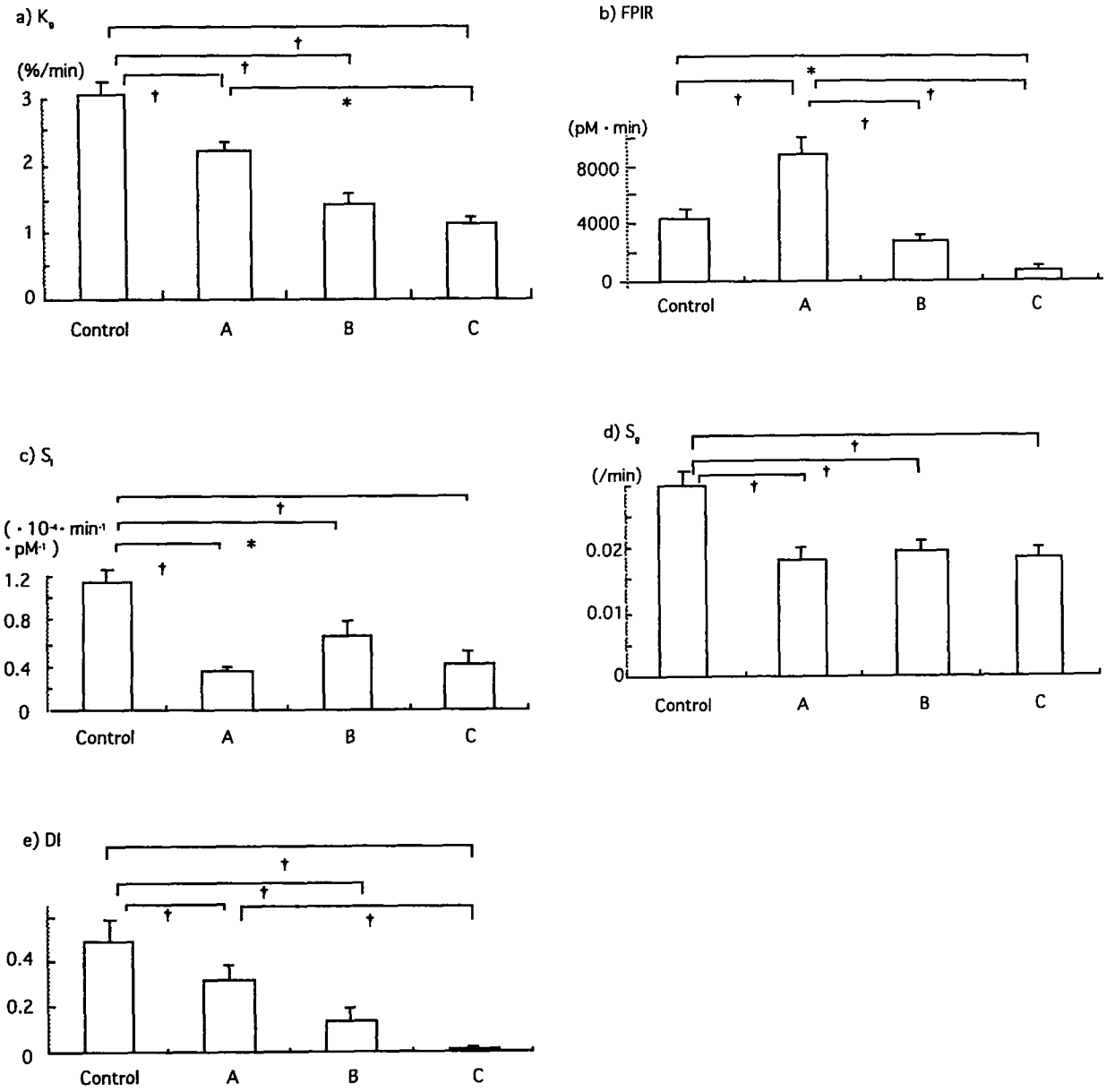

Fig 1. Difference in K_g, FPIR, S_I, S_g, and DI among the 3 obese groups (A, nondiabetic; B, diabetes without drugs; C, diabetes with a history of treatment with hypoglycemic agents) and the non-obese controls. *$P < .05$, †$P < .01$. Results are the mean ± SE.

Table 2. Analytical Parameters From FSIGT With Minimal Model Analysis (mean ± SE)

Parameter	(A) Simple Obesity	(B) Obese Type 2 Diabetes on Diet Only	(C) Obese Type 2 Diabetes With Hypo Agent	P A v B	P A v C	P B v C	P ANOVA	Non-obese Controls
K_g (%/min)	2.13 ± 0.19†	1.46 ± 0.10†	1.17 ± 0.11†	NS	.012	NS	.0006	3.02 ± 0.25
S_g (/min)	0.017 ± 0.002†	0.018 ± 0.002†	0.017 ± 0.002†	NS	NS	NS	NS	0.030 ± 0.003
S_I ($\cdot 10^{-4}$ · min · pmol/L)	0.378 ± 0.060†	0.650 ± 0.213*	0.450 ± 0.182†	NS	NS	NS	NS	1.123 ± 0.132
FPIR (pmol/L · min)	9,355 ± 1,386†	2,825 ± 1,054	852 ± 410*	<.0001	<.0001	NS	<.0001	4,688 ± 552
DI	0.286 ± 0.044†	0.138 ± 0.051†	0.025 ± 0.010†	NS	.005	NS	.0006	0.481 ± 0.059
BIE (/min)	0.004 ± 0.001*	0.006 ± 0.001	0.004 ± 0.001	NS	NS	NS	NS	0.007 ± 0.001
GEZI (/min)	0.013 ± 0.002†	0.011 ± 0.002†	0.014 ± 0.002*	NS	NS	NS	NS	0.023 ± 0.003

Abbreviation: Hypo, hypoglycemic.
*$P < .05$ v control.
†$P < .01$ v control.

the obese groups, although the difference between groups B and C did not reach statistical significance (Figs 1e and 2). There were also significant differences in the DI between the non-obese controls and the 3 obese groups (each $P < .01$).

There was a statistically significant difference in FPG ($P = .0014$) among the obese groups, although the difference between groups B and C did not reach statistical significance. FPG also did not differ significantly between group A and the non-obese controls. The Ib value was significantly lower in group C than in group B, while Ib values were higher among the 3 obese groups versus the non-obese controls (Table 1). The BIE, Ib × S_I, was significantly decreased only in group A compared with the non-obese controls ($P < .05$). There were no statistically significant differences in the BIE among the 3 obese groups. GEZI, S_g − BIE, was significantly decreased in the obese groups compared with the non-obese controls (each $P < .05$), but did not differ significantly among the 3 obese groups, as well as S_g or the BIE (Table 2).

K_g as a dependent variable was explained by a multiple stepwise regression analysis as follows: $K_g = 2.116 \times 10^{-4}$ DI ($P = .028$) −0.014 FPG + 25.959 GEZI + 2.367 ($P = .011$; $R^2 = 71\%$) in the 3 obese groups, and $K_g = 3.629 \times 10^{-4}$ DI ($P < .0001$) −0.007 OI − 75.885 BIE + 1.705 ($R^2 = 71\%$) in all subjects including the non-obese controls.

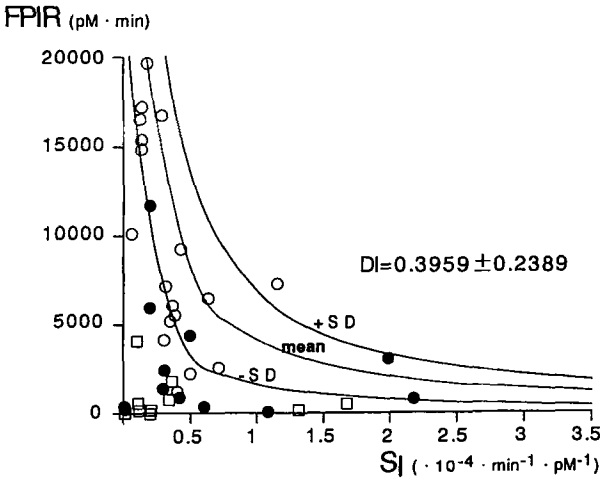

Fig 2. Relationship between S_I and FPIR in the 3 obese groups (A, nondiabetic, ○; B, diabetes without drugs, ●; C, diabetes with a history of treatment with hypoglycemic agents, □. The reference range of a hyperbolic relation of the DI (mean ± SD) was obtained from 70 subjects with normal glucose tolerance.

DISCUSSION

The present study found a concomitant decrease in the DI, FPIR × S_I, with the progression to diabetes and a severity that was characteristic of obese Japanese adolescents. This decrease was likely largely due to the decrease in FPIR, since S_I did not differ among any of the obese groups in the present study. In addition, S_g was significantly lower in each obese group than in the nondiabetic control subjects, suggesting the predisposition to glucose intolerance. However, this did not differentiate according to the severity of the disease.

Glucose tolerance may be considered to be related to 3 major factors, including insulin secretion, or FPIR, S_I, and S_g in a FSIGT according to a minimal model analysis. As expected, values for S_I were lower in the obese groups versus the non-obese controls, but did not differ significantly among the 3 obese groups. The lower S_I may be explained by the fact that insulin resistance is exaggerated during puberty, as reported previously.[23-26] Since the change in S_I itself may have some effect on the decrease in the DI, the lower S_I may also be involved in the progression to type 2 diabetes in Japanese adolescents.

S_g reflects the ability of cells to increase glucose uptake and suppress endogenous output in response to changes in glucose levels independently of changes in insulin levels. In the present study, S_g in group A with simple obesity was lower than that in non-obese controls. Cook et al[23] also reported a negative relation between the BMI and S_g in adolescent subjects. Furthermore, S_g was significantly higher in prepubertal children at Tanner stage 1 than in adolescents at Tanner stages 2 to 4 (0.046 v 0.030/min) in our previous study.[14] Cook et al[23] also showed a gradual but not statistically significant decline in S_g from Tanner stages 1 to 5. Since S_g may be improved only by continuous exercise as reported previously,[27,28] the low S_g may derive from the low physical activity in obese adolescents. As for the racial or genetic predisposition of Japanese people, the low S_g was observed in nondiabetic offspring of patients with type 2 diabetes,[11] subjects with IGT,[9,10] and non-obese subjects with type 2 diabetes (NIDDM).[8] Since S_g accounts for approximately 50% of glucose disposal during a glucose load in normal subjects,[29] the low S_g may result in glucose intolerance. Therefore, we conclude that obese Japanese adolescents, to a

certain degree, may have a higher risk for glucose intolerance due to low S_g even before the progression to type 2 diabetes. However, S_g may not affect the severity to the same degree as found in this study and the report from Osei et al.[7]

The value for Ib was higher in each obese group versus the non-obese controls, although the value was significantly lower in group C than in group B. The urine C-peptide level in groups B and C remained within the reference range (Table 1). Thus, Ib or urine C-peptide was not a marker for the progression to diabetes and did not differentiate according to the severity of diabetes. Furthermore, neither the BIE nor GEZI differentiated according to the severity of diabetes (Table 2).

In relation to S_I, the role of endogenous insulin secretion or the response to glucose stimulation may be essential in the progression to type 2 diabetes and its severity in Japanese adolescents. The DI reflects the insulin effect as a hyperbolic relationship between S_I and FPIR in a FSIGT using minimal model analysis.[22] Accordingly, the decrease in the DI reflected the progression to diabetes and its severity (Figs 1e and 2). The decrease in the DI was likely largely due to the decrease in FPIR, since S_I did not differ significantly among the 3 obese groups in this study. This finding is consistent with the report by Osei et al,[7] who showed a decrease in the DI in response to a corresponding decrease in FPIR along with the progression to severe diabetes, regardless of any change in S_I. An insufficient compensation in FPIR was recognized before the progression to diabetes mellitus, as found both in subjects with IGT in their study[7] and in group A adolescent subjects with simple obesity in the present study. Furthermore, it is likely that FPIR reflects the β-cell dysfunction specifically in terms of glucose rather than nonglucose secretagogues in obese Japanese adolescents with type 2 diabetes, since Ib and urine C-peptide did not differ statistically among any of the obese groups. Thus, we suggest that the DI may be a marker of the insulin effect largely due to β-cell dysfunction to glucose stimulation along with the progression to diabetes and its severity in a population of obese Japanese adolescents.

Taken as a whole, these results show that obese Japanese adolescents may have a risk for glucose intolerance. Regarding the precipitating factors in the progression to diabetes, type 2 diabetes requires various degrees of insulin secretory insufficiency with insulin resistance.[13] Groups A, B, and C in the present study had essentially the same degree of insulin resistance as detected by S_I, and the same secretory capacity of insulin as detected by Ib. S_g values were also low in the 3 obese groups. In addition, clinical characteristics such as the degree of obesity and age at diabetes onset were essentially similar between groups B and C. Thus, we suggest that the 3 obese groups, as a whole, can be considered as sequential clinical stages of glucose intolerance in the same category of type 2 diabetes. In contrast, the difference in the severity of diabetes depended on the FPIR or DI. Furthermore, the DI in group A with simple obesity was also significantly lower versus the control subjects. Since it is the case that the more severe the patient's diabetes, the higher the percentage of diabetics in his or her first-degree relatives (Table 1), the genetic influence may be considered in decreasing the FPIR or DI. Although some subjects in group A may sequentially develop the clinical stages to inclusion in groups B and C, it has not been proven in the present cross-sectional study. Yokoyama et al[30] reported that prolonged inadequate treatment of and a family predisposition to diabetes led to a rapid-onset of severe diabetic complications and an insulin requirement in Japanese early-onset type 2 diabetes, although these patients continued to show some residual β-cell reserves as detected by the serum C-peptide level.

Here, we should consider the classification of diabetes in the present patients, especially in terms of group C. Patients in the present study showed clinical similarities in obesity, diabetic ketoacidosis, and acanthosis nigricans, as well as similarly high levels of basal serum insulin, compared with youth-onset diabetic African-American patients reported by Scott et al.[4] Whereas Scott et al classified obese diabetic patients, even those with ketosis or ketoacidosis at onset, as NIDDM according to the definition of the World Health Organization Expert Committee on Diabetes in 1985, a certain percentage of African-American patients with ketosis at onset might now be classified as type 1 diabetes, according to the report of the American Diabetes Association in 1997.[13] Although we have classified our obese diabetic adolescents, including group C, as type 2 diabetics at the present time, the classification of youth-onset obese diabetic patients for each ethnic group requires further etiologic research and a more precise definition according to the American Diabetes Association in 1997[13,31] and the World Health Organization in 1998.[32]

In conclusion, an early manifestation of type 2 diabetes with occasional ketosis at onset may result from β-cell dysfunction to glucose stimulation, as demonstrated by a relatively low FPIR to decreased S_I in obese Japanese adolescents, as well as a low S_g as a synergic role in glucose intolerance. Such pathogenic factors arising from a racial or constitutional predisposition may be involved as additional precipitating factors to obesity in the application of the "thrifty genes" hypothesis[5] in obese Japanese adolescents.

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