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Predictors of glycemic control in Japanese subjects with type 2 diabetes mellitus

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Abstract

The purpose of this study was to investigate which pathophysiological and demographic characteristics of Japanese subjects with type 2 diabetes mellitus were associated with poor glycemic control and to propose a statistical model for predicting their glycemic control. A total of 220 subjects with type 2 diabetes mellitus were enrolled in this study. Frequently sampled intravenous glucose tolerance test was performed to determine the first-phase C-peptide secretion rate (CS1) and insulin sensitivity index. Multiple regression analysis in a stepwise manner was carried out to identify independent regulators of glycemic control. Upon stepwise linear regression analysis with hemoglobin A_{1c} as a dependent parameter, fasting plasma glucose concentration (FPG), CS1, and onset age remained as predictors, explaining 41.0% of glycemic control. The young-onset group (onset age ≤48 years) had significantly higher hemoglobin A_{1c} than the old-onset group (onset age >48 years) ($P = .0148$), although the present age was significantly older in the old-onset group; and there were no significant differences in duration of diabetes, treatment, body mass index, FPG, fasting insulin level, homeostasis model assessment of insulin resistance, CS1, and log(insulin sensitivity index) between them. Worsening factors of glycemic control in Japanese subjects with type 2 diabetes mellitus were elevated FPG, impaired first-phase insulin secretion, and young age of onset of the disease. Because glycemic control in the subjects with young-onset diabetes tends to be worse, early and aggressive intervention should be required for those with young-onset diabetes to prevent long-term complications.

1. Introduction

Since the Diabetes Control and Complication Trial and the United Kingdom Prospective Diabetes Study demonstrated that excellent glycemic control reduces microvascular complications in types 1 and 2 diabetes mellitus, respectively [1,2], glycated hemoglobin has become an increasingly important measure of glycemic control. Despite the strong consensus that excellent glycemic control improves microvascular outcomes in type 2 diabetes mellitus [3], there are limited numbers of patients with diabetes who can obtain good glycemic control. Identifying pathophysiological, treatment, and demographic parameters that predict poor control may improve outcomes by allowing better matching of patients to compensatory interventions.

Impaired insulin secretion and impaired insulin action are the 2 major components contributing to the pathophysiology of type 2 diabetes mellitus [4]. A previous study demonstrated that defective insulin secretion plays a predominant role in the development of type 2 diabetes mellitus in the Japanese population [5], in contrast to insulin resistance having an important role in the development of diabetes in white subjects [6]. Recently, a longitudinal study revealed that insulin sensitivity declined over time and that the loss of compensatory increase in insulin secretion led to deterioration of glucose tolerance in African American, Hispanic, and non-Hispanic white subjects [7].

Previously, we proposed a combined method of 2-compartment model of C-peptide kinetics [8] and minimal model analysis [9] by frequently sampled intravenous glucose tolerance test (FSIGT) to assess the β-cell function, insulin sensitivity, and insulin-independent glucose disposal [10]. In the present study, using the parameters obtained from this method and demographic parameters, we tried to assess

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which characteristics of Japanese subjects with type 2 diabetes mellitus were associated with poor glycemic control and to propose a statistical model for predicting their glycemic control. In addition, we demonstrate that age at onset, ability of insulin secretion, and fasting glucose concentration predict glycemic control in Japanese subjects with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Subjects

We recruited 220 (male-female, 146/74) subjects with type 2 diabetes mellitus at the Diabetes Center, Chiba Central Medical Center, Chiba, Japan. All the subjects enrolled in this study were ethnic Japanese. Diabetes mellitus was diagnosed according to the 1985 World Health Organization criteria [11]. All patients tested were negative for anti–glutamic acid decarboxylase. The treatment of diabetes for the initial 2 years was diet or oral agents for all the subjects. Before participation, the purpose and risk of the study were explained; and informed consent was obtained from all the participants. The protocol was approved by the ethics committee of Chiba Central Medical Center.

2.2. C-peptide secretion rate and minimal model analysis

To examine the reserve of insulin secretion, insulin sensitivity, and glucose effectiveness, a combined method of 2-compartment model of C-peptide kinetics and minimal model approach in FSIGT was performed according to the protocol described before [10,12]. The first-phase C-peptide secretion rate (CS1) was determined by the sum of the C-peptide secretion rate from 0 to 5 minutes after intravenous glucose load. The CS1 is 6.8 to 18.5 ng/mL per 5 minutes (mean ± SD, 10.8 ± 3.9) in subjects with normal glucose tolerance without diabetic patients in their family. The insulin sensitivity index (Si) and glucose effectiveness (Sg) were calculated using the glucose and insulin concentrations by the minimal model software program, which we developed according to the algorithm described by Pacini et al [13]. The Si and Sg are 2.6 to 7.6 × 10^{-4} min^{-1} per μU/mL (4.59 ± 1.76) and 1.15 to 4.1 × 10^{-2}/min (2.56 ± 0.92), respectively, in subjects with normal glucose tolerance without diabetic patients in their family.

2.3. Statistical analysis

Data are means ± SD. Parameter Si was log transformed because it was not normally distributed. The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated with the following formula: fasting insulin (in microunits per milliliter) × fasting glucose (in micrograms per deciliter)/405. Multiple regression analysis in a stepwise manner was carried out to identify independent regulators of glycemic control. To investigate the relationship between the age at onset of type 2 diabetes mellitus and glycemic control (hemoglobin A_{1c} [HbA_{1c}]), we divided the study subjects whose duration period was within 10 years into young-onset (onset age ≤48 years) and old-onset (onset age >48 years) subgroups. The cutoff value was obtained by using the mean value of onset age of the total subjects (mean onset age = 48.2 years). Comparisons between groups were performed by means of unpaired Student t test and simple χ^2 test. The Spearman coefficient was used to examine correlations. Statistical significance was defined as P value < .05. The software package JMP version 6 (SAS Institute, Cary, NC) was used for all computations.

3. Results

3.1. Characteristics of the subjects

Table 1 summarizes the clinical characteristics and measures of variables obtained in FSIGT in diabetic subjects. First-phase C-peptide secretion rate in FSIGT was extremely low in most diabetic subjects in this study (range, 0-7.127 ng/mL per 5 minutes) compared with the reference range in the subjects with normal glucose tolerance. In contrast, Si and Sg values in diabetic subjects were distributed in a wide range (range, 0.0013-9.17 × 10^{-4} min^{-1} per μU/mL for Si and 0-6.41 × 10^{-2}/min for Sg).

3.2. Correlation of glycemic control (HbA_{1c}) to measures of variables

Hemoglobin A_{1c} had strong negative correlation to onset age, CS1, and insulin sensitivity (logSi) and strong positive correlation to fasting plasma glucose (FPG), duration of diabetes, and HOMA-IR (Table 2). Upon stepwise linear regression analysis with HbA_{1c} as a dependent parameter, FPG, CS1, and onset age remained as predictors, explaining 41.0% of the variance of glycemic control (Table 3). If FPG was removed from the analysis, CS1 (P < .0001), onset age (P < .0001), and logSi (P = .036) remained as predictors, explaining only 18.3% of the variance of glycemic control (R^2 = 0.183).

Table 1
Clinical characteristics and measures of variables obtained in FSIGT

	Total
N	220
Female-male	74/146
Age (y)	56.4 ± 12.9 (19~88)
Onset age (y)	48.2 ± 12.6 (12~78)
Duration (y)	8.24 ± 7.75 (0~40)
BMI (kg/m^2)	24.5 ± 3.80 (14.4~38.9)
HbA_{1c} (%)	7.79 ± 1.80 (4.6~16.4)
Treatment (diet/OHA/insulin)	70/84/66
FPG (mg/dL)	154.2 ± 50.3 (47~308)
IRI (μU/mL)	9.61 ± 11.01 (1~84)
HOMA-IR	3.83 ± 5.49 (0.17~40.6)
CS1 (ng/mL per 5 min)	1.02 ± 1.00 (0.00~7.12)
Log(Si × 10^4)	0.086 ± 0.56 (−2.88~0.96)
Si (×10^{-4} min^{-1} per μU/mL)	2.15 ± 2.08 (0.0013~9.17)
Sg (×10^{-2}/min)	1.65 ± 0.96 (0~6.41)

Data are means ± SD. OHA indicates oral hypoglycemic agent.

Table 2
Correlation of HbA_{1c} to clinical characteristics and measures of variables obtained in FSIGT (Spearman correlation coefficient)

	HbA_{1c}	
	r	*P*
Age	−0.0403	.5524
Onset age	−0.1886	.0050
BMI	0.0490	.4698
Duration	0.3094	<.0001
FPG	0.6187	<.0001
IRI	0.0471	.4874
HOMA-IR	0.2797	<.0001
CS1	−0.3187	<.0001
LogSi	−0.2365	.0004
Sg	0.0081	.9048

3.3. Correlation among the variables

Among the variables, strong correlations were seen between FPG and duration ($r = 0.1842$, $P = .0061$), FPG and HOMA-IR ($r = 0.4263$, $P < .0001$), FPG and CS1 ($r = -0.3391$, $P < .0001$), FPG and logSi ($r = -0.2973$, $P < .0001$), CS1 and body mass index (BMI) ($r = 0.2743$, $P < .0001$), CS1 and duration ($r = -0.2711$, $P < .0001$), CS1 and fasting insulin (IRI) level ($r = 0.2220$, $P = .0009$), and onset age and duration ($r = -0.2776$, $P < .0001$).

3.4. Comparison of clinical features between young-onset and old-onset subgroups

As shown in Table 4, the study subjects whose duration period were within 10 years were divided into young-onset (onset age ≤48 years) subgroup including 68 subjects and old-onset (onset age >48 years) subgroup including 96 subjects. Present age in old-onset subgroup was significantly older compared with the young-onset subgroup ($P < .0001$). Hemoglobin A_{1c} was significantly higher in young-onset group ($P = .0148$). There were no significant differences in duration of diabetes, treatment, BMI, FPG, IRI level, HOMA-IR, CS1, logSi, and Sg.

4. Discussion

The present study tried to find which variables in demographic and pathophysiological characteristics were most significant to explain the variance of glycemic control in the Japanese subjects with type 2 diabetes mellitus. In addition, we demonstrated that FPG, CS1, and age of diabetes onset were independent determinants of glycemic control.

Table 3
Stepwise linear regression of independent variables associated with HbA_{1c}

Independent variables	Parameter estimate	SE	*P*
Intercept	6.472	0.565	<.0001
CS1	−0.3449	0.1000	.0007
FPG	0.01878	0.00198	<.0001
Onset age	−0.02525	0.00765	.0011

Independent variables: sex, age, onset age, duration of diabetes, BMI, FPG, IRI, CS1, logSi, Sg; 0.25 significant level for entry of variables into the model. Dependent variable = HbA_{1c}. $R^2 = 0.410$.

Table 4
Comparison of clinical characteristics and measures of variables obtained in FSIGT between young-onset and old-onset subjects whose duration periods were within 10 years

	Young onset	Old onset
n	68	96
Female-male	15/53	41/55
Age (y)	43.1 ± 10.6	62.8 ± 7.3 *
Onset age (y)	38.08 ± 9.69	58.49 ± 6.61 *
Duration (y)	5.04 ± 3.74	4.33 ± 3.60
BMI (kg/m^2)	25.38 ± 4.33	24.48 ± 3.57
HbA_{1c} (%)	8.10 ± 2.15	7.32 ± 1.73 *
Treatment (diet/OHA/insulin)	26/25/17	38/33/25
FPG (mg/dL)	155.8 ± 50.2	148.0 ± 47.9
IRI (μU/mL)	9.61 ± 11.2	9.44 ± 11.0
HOMA-IR	3.92 ± 5.99	3.68 ± 5.05
CS1 (ng/mL per 5 min)	1.35 ± 1.52	0.97 ± 0.63
Log($Si \times 10^4$)	0.148 ± 0.471	0.092 ± 0.558
Sg ($\times 10^{-2}$/min)	1.81 ± 1.13	1.65 ± 0.93

Data are means ± SD.
* $P < .05$.

Hemoglobin A_{1c} had the strongest correlation to FPG. Stepwise regression analysis revealed that FPG was an independent determinant of HbA_{1c}, although FPG, HOMA-IR, and logSi were correlated with each other. In the fasting state, insulin regulation of hepatic and renal endogenous glucose production (EGP) is the major factor determining plasma glucose concentrations because most tissue glucose uptake occurs by insulin-independent mechanisms [14,15]. Although HOMA-IR and Si represent the insulin resistance and insulin sensitivity, both terms have different implications. The HOMA-IR, which is solely based on FPG and IRI, may therefore primarily be an index of the resistance of EGP to suppression by insulin [16], whereas the studies using FSIGT measured the overall insulin sensitivity including the ability of insulin to suppress the basal state glucose production and insulin-stimulated muscle glucose uptake. Therefore, the finding that FPG was a predictor of HbA_{1c} would indicate the significance of EGP in glycemic control in Japanese subjects with type 2 diabetes mellitus and reconfirm that FPG is a good surrogate measure of glycemic control.

Type 2 diabetes mellitus results from a combination of impaired insulin secretion and insulin resistance [4]. Which of these factors represents the primary pathogenesis of the disease depends on individuals or ethnicity [5,6,17]. In the present study, most diabetic subjects exhibited decreased insulin secretion (CS1) and varied range of insulin sensitivity, consistent with previous work [6,7,12], demonstrating that defective insulin secretion plays a predominant role in the pathogenesis of diabetes in Japanese, whereas insulin resistance play a more important role in white subjects [17,18]. In the present study, FPG and CS1 in the

pathophysiological parameters were identified as independent predictors of glycemic control, suggesting that hepatic glucose overproduction and impaired first-phase insulin secretion play an important role in the progression of diabetes. This observation leads to the idea that treatment to suppress EGP and to improve first-phase insulin secretion would be most effective for Japanese patients with type 2 diabetes mellitus.

The present study revealed that the age of diabetes onset was a significant predictor of glycemic control and that it was more difficult to stabilize glycemic control in younger-onset patients despite uniform protocol for treatment titration, consistent with previous work [19–21]. Elgzyri et al [22] followed more than a thousand type 2 diabetes mellitus patients for 7 years after diagnosis and demonstrated that age at diagnosis showed a significant influence on HbA_{1c} change over time. They showed that patients younger than 50 years at diagnosis of type 2 diabetes mellitus experienced steeper increase in HbA_{1c} than did those 50 years or older at diagnosis.

The glycemic control was worse in the young-onset diabetes group compared with the old-onset group even after adjusting for the duration of diabetes. Type 2 diabetes mellitus is thought to be a complex polygenic disorder that arises as predisposing environmental factors interact with many genetic variants [23], in contrast to rare monogenic forms of early-onset non–type 1 diabetes mellitus, such as maturity-onset diabetes of the young and mitochondrial diabetes. A recent study showed that strong family history predicted younger age of onset for subjects diagnosed with type 2 diabetes mellitus [24]. Thus, it is possible that because of profound involvement of genetic factor, the young-onset diabetes tends to progress rapidly irrespective of the mode of treatment. Moreover, in young-onset diabetes, environmental factors often observed in young Japanese adults, such as reduced exercise, overeating, increased stress in the job, depression, and others, would deteriorate the glycemic control progressively.

In the present study, there was no difference in BMI between the young-onset and old-onset groups. A population-based study among those newly diagnosed with type 2 diabetes mellitus in adults in the United States including 90% non-Hispanic white subjects showed an inverse linear relationship between BMI and age of diabetes onset, suggesting that obesity is a risk for diabetes onset [21]. This discrepancy may result from the different pathogenesis for diabetes between Japanese and white subjects.

In conclusion, worsening factors of glycemic control in Japanese subjects with type 2 diabetes mellitus were elevated FPG, impaired first-phase insulin secretion, and young age of onset of the disease. Therefore, to suppress EGP and to improve first-phase insulin secretion would be the most effective treatment for Japanese patients. Because glycemic control in the subjects with young-onset diabetes tends to be worse than in those with old-onset diabetes despite identical treatment and follow-up protocol, early and aggressive intervention should be required for those with young-onset diabetes to prevent long-term complications.

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