ISSN 2472-1972

Clinical Significance of the Maximum Body Mass Index Before Onset of Type 2 Diabetes for Predicting Beta-Cell Function

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Abstract

Objective: This study aimed to clarify the clinical significance of the maximum body mass index (BMI) before the onset of type 2 diabetes (MBBO) for predicting pancreatic beta-cell function.

Methods: This was a cross-sectional observational study. Of 1304 consecutively admitted patients with type 2 diabetes, we enrolled 410 patients satisfying the criteria in this study. The correlations between the C-peptide index (CPI), which is one of the parameters that reflects beta-cell function, and various clinical parameters, including MBBO and duration of diabetes, were analyzed in multiple linear regression analyses.

Results: The analyses revealed that MBBO was correlated with CPI independently after adjustment for age, sex, HbA1c, and duration of diabetes. When we divided the subjects into three subgroups by MBBO (MBBO < 25 kg/m^2; 25 kg/m^2 ≤ MBBO < 30 kg/m^2; MBBO ≥ 30 kg/m^2), CPI was negatively correlated with duration of diabetes in each subgroup, while the rates of CPI based on the duration of diabetes were not different among the three MBBO subgroups. In contrast, the declining rates of CPI were higher in the BMI ≥ 25 kg/m^2 group on admission than in the BMI < 25 kg/m^2 group on admission.

Conclusions: MBBO may be an independent factor correlating with beta-cell function and may predict insulin secretion capacity at diagnosis, but it does not seem to affect the rate of decline in insulin secretion capacity after diagnosis. It is important to preserve beta-cell function by decreasing a patient's BMI during treatment after diagnosis regardless of MBBO.

Key Words: type 2 diabetes, obesity, insulin secretion capacity

1. Introduction

Type 2 diabetes is characterized by both insulin resistance and beta-cell dysfunction (1). Insulin resistance is mainly caused by overweight or visceral fat accumulation generated from patient lifestyles (2, 3), while beta-cell function in individuals is determined by genetic factors (4). It has been reported that the insulin secretion capacity of patients with type 2

Received 30 May 2019
Accepted 23 February 2020
First Published Online 13 March 2020
Corrected and Typeset 13 March 2020.

diabetes declines progressively with the duration of diabetes (5), and some previous reports have suggested that a high body mass index (BMI) during treatment for diabetes is associated with a high rate of decline in insulin secretion capacity in the patient (6, 7).

In contrast, in prediabetes, beta cells increase insulin secretion in response to insulin resistance to maintain plasma glucose at a normal level (1); thus, the degree of insulin resistance could also represent the insulin secretion capacity. Since BMI is the major determinant of insulin resistance (8), BMI should also be an indicator of beta-cell function in individuals with prediabetes (9). Physicians often inquire regarding the maximum BMI before type 2 diabetes onset, but the clinical significance of this parameter is not necessarily clear. Although several studies have described the relationship between the BMI of patients with type 2 diabetes mellitus and the rate of decline in beta-cell function, it seems difficult to use the BMI of patients with type 2 diabetes mellitus as an indicator of beta-cell function. This is because their BMI would be affected by medications for the treatment of glycemic control. Considering that BMI should be an indicator of beta-cell function in patients with prediabetes, the maximum BMI before onset of diabetes (MBBO) might reflect the maximum beta-cell function that the patient had ever possessed. Thus, we thought that this parameter, MBBO, could express the potential function of beta cells in patients. However, few clinical studies have been conducted to evaluate whether MBBO is associated with insulin secretion capacity.

The purpose of this study was to examine whether MBBO can act as an indicator of beta-cell function in patients with type 2 diabetes mellitus. We enrolled diabetic patients admitted to our hospital and analyzed the correlations between their MBBO and various clinical parameters, including insulin secretion capacity, in a multiple regression analysis. We also investigated whether MBBO may be an independent factor predicting the beta-cell function of the patient and whether it might affect the rate of decline in insulin secretion capacity after diagnosis during the treatment of diabetes.

2. Materials and Methods

A. *Study population*

We retrospectively reviewed 1304 consecutive patients with type 2 diabetes who were admitted to Osaka University Hospital between August 1, 2010, and June 30, 2017, for treatment of poor glycemic control. Data for the present study were obtained from the medical records of Osaka University Hospital. The patient flow diagram is shown in Fig. 1. A total of 58 subjects were excluded because their maximum BMI was not recorded; 298 subjects whose maximum BMI was reached after the diagnosis of type 2 diabetes mellitus were also excluded. We excluded these subjects because we could not identify their maximum BMI before onset and considered that in those patients, the maximum BMI after the development of type 2 diabetes mellitus was affected by the use of hypoglycemic agents and/or insulin and would not indicate the patients' potential beta-cell function. Furthermore, 185 patients with cancer, 51 patients with pancreatic diseases, 14 patients with liver cirrhosis, 82 patients taking diabetogenic medicines such as glucocorticoids, 126 patients with an additional secondary form of diabetes, 11 patients who had pregestational diabetes mellitus, and 36 patients with diabetes-related autoantibodies, including antibodies against glutamic acid decarboxylase, insulin, and insulinoma-associated protein 2, were excluded. In addition, 33 patients whose estimated glomerular filtration rate was less than 30 mL/min/1.73 m^2 were excluded because the turnover of serum C-peptide immunoreactivity (CPR) is prolonged due to decreased renal function (10). Finally, 410 patients were enrolled in this study.

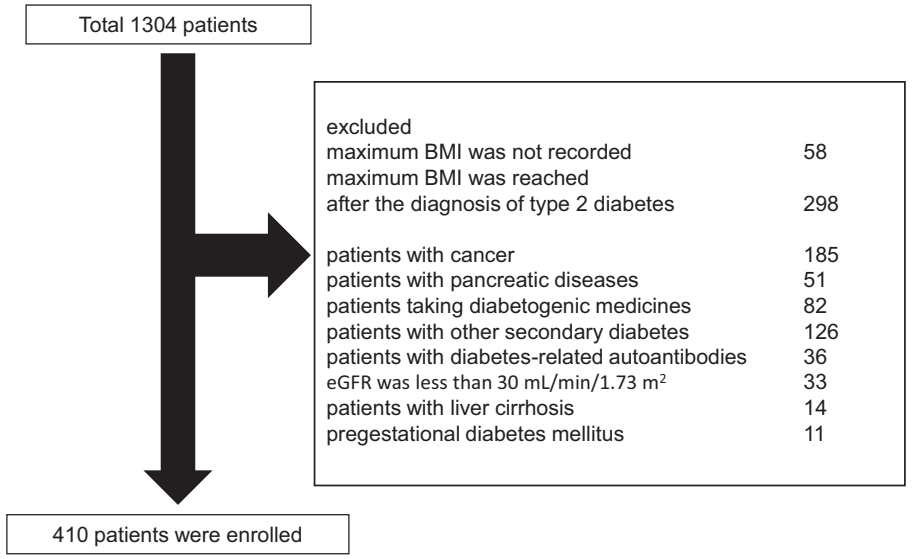

Figure 1. Patient flow diagram.

B. *Study protocol*

After admission, most of the patients were treated by medical nutrition therapy plus bolus insulin therapy to improve preprandial plasma glucose levels, including fasting plasma glucose (FPG), the target level of which was below 8.4 mmol/L. We performed a blood evaluation before breakfast 12 hours after the last meal. Some of the patients were also treated with additional oral hypoglycemic agents or basal insulin. After glycemic control was almost maintained at the target levels, beta-cell function was evaluated. Beta-cell function was evaluated using the C-peptide index (CPI), which was calculated by using the following formula: F-CPR (ng/mL) × 100 / FPG (mmol/l) × 18. We previously demonstrated significant positive correlations between the relative beta-cell area, indicating beta-cell mass, and various parameters of insulin secretory capacity, including CPI (11). FPG was 7.4 ± 1.7 mmol/L at evaluation. The medications used as glucose-lowering agents before admission and at evaluation are described in Table 1. We defined the onset of type 2 diabetes mellitus as occurring when the patients had been diagnosed with type 2 diabetes mellitus based on the criteria of the American Diabetes Association (12) or started to take glucose-lowering agents. Based on their history of maximum BMI and the age at diabetes mellitus onset, we defined their MBBO.

This study was approved by the institutional ethics review board of Osaka University Hospital and was carried out in accordance with the principles of the Declaration of Helsinki. The study was announced to the public on the website of our department at Osaka University Hospital, and all patients were allowed to participate or refuse to participate in the study.

C. *Statistical analyses*

We summarize the background variables as the mean +/– standard deviation (SD) for continuous variables and as the counts with proportions for categorical variables. We considered 3 groups based on the MBBO (low group: MBBO < 25 kg/m^2, intermediate group: 25 kg/m^2 ≤ MBBO < 30 kg/m^2, high group: 30 kg/m^2 ≤ MBBO), and the background variables are also presented as medians (interquartile range) for the continuous variables and as counts with proportions for the categorical variables according to MBBO group. The continuous and categorical variables were compared among the 3 MBBO groups using the Kruskal–Wallis test and chi-squared test, respectively.

Table 1. Clinical characteristics of the study subjects

MBBO	All (n = 410)	MBBO < 25 (n = 75)	25 ≦ MBBO < 30 (n = 164)	30 ≦ MBBO (n = 171)	P value
Age (years)	61 ± 14	67 (61~74)	65 (58~74)	56 (45~67)	<.0001
Sex (M / F)	243 / 167	44/31	96 / 68	103 / 68	.94
Age at diagnosis of T2DM (years)	50 ± 13	56 (47~64)	54 (45~62)	44 (36~53)	<.0001
Duration (years)	11 ± 10	10 (1~17)	10 (1.6~18)	10 (3~16)	.99
BMI on admission (kg/m^2)	25.8 ± 5.2	20.9 (18.7~22.1)	24.0 (22.4~25.5)	29.0 (26.3~32.3)	<.0001
MBBO (kg/m^2)	29.9 ± 6.0	23.2 (21.6~24.3)	27.1 (26.2~28.4)	34.1 (31.8~38.1)	<.0001
Age at MBBO (years)	38 ± 14	35 (20~50)	40 (30~53)	35 (26~42)	<.0001
HbA1c (%)	9.0 ± 1.9	8.3 (7.5~9.9)	8.3 (7.7~9.7)	8.9 (8.0~10.5)	.0058
HbA1c (mmol/mol)	75 ± 20	67 (58~85)	67 (61~82)	74 (64~91)	.0098
FPG (mmol/l)	7.4 ± 1.7	7.3 (6.1~8.3)	7.4 (6.4~8.6)	7.1 (6.2~8.4)	.70
CPI	1.3 ± 0.8	0.77 (0.47~1.1)	1.1 (0.75~1.6)	1.3 (0.86~2.0)	<.0001
Medication before admission					
Sulfonylurea	159 (38.8%)	34 (45.3%)	64 (39%)	61 (35.7%)	.36
Glinide	11 (2.7%)	1 (1.3%)	4 (2.4%)	6 (3.5%)	.60
Biguanide	102 (24.9%)	11 (14.7%)	33 (20.1%)	58 (33.9%)	.0011
TZD	34 (8.3%)	5 (6.7%)	12 (7.3%)	17 (9.9%)	.58
α-GI	71 (17.3%)	9 (12%)	34 (20.7%)	28 (16.4%)	.23
DPP-4i	145 (35.4%)	32 (42.7%)	51 (31.1%)	62 (36.3%)	.21
SGLT2i	10 (2.4%)	0 (0%)	1 (0.6%)	9 (5.3%)	.0070
GLP-1RA	17 (4.1%)	0 (0%)	3 (1.8%)	14 (8.2%)	.0019
Insulin	108 (26.3%)	18 (24.0%)	38 (23.2%)	52 (30.4%)	.29
No medication	87 (21.2%)	15 (20.0%)	39 (23.8%)	33 (19.3%)	.58
Medication at evaluation					
Insulin secretagogues	61 (14.9%)	9 (12.0%)	22 (13.4%)	30 (17.5%)	.42
NPH or LAI	185 (45.1%)	29 (38.7%)	61 (37.2%)	95 (55.6%)	.0015

Data are reported as the mean ± SD, median (interquartile range), or n (%), unless otherwise indicated. Comparisons among the three groups divided by MBBO were performed by a Kruskal–Wallis test or a χ^2 test for data presented as the median (interquartile range) or n (%), respectively. P values < .05 were considered statistically significant. Insulin secretagogues include sulfonylurea, glinide, DPP-4i, and GLP-1RA.

Abbreviations: α-GI, alpha-glucosidase inhibitor; BMI, body mass index; CPI, C-peptide index; DPP-4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor antagonist; LAI, long-acting insulin; MBBO, maximum BMI before onset; NPH, neutral protamine Hagedorn;SGLT2i, sodium glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione.

Univariate and multivariate linear regression analyses were conducted to evaluate associations between CPI and duration of diabetes and between CPI and MBBO groups or BMI groups (low group: BMI < 25 kg/m^2, high group: 25 kg/m^2 ≤ BMI). In the multivariate analyses, we evaluated the relationship between CPI and the duration of diabetes adjusted by age, sex, HbA1c, and group (MBBO groups or BMI groups). To elucidate whether high MBBO or high BMI on admission was associated with high CPI, the impact of the MBBO groups or BMI groups on CPI was also assessed in the same multivariate analyses.

To investigate whether the rate of decline in CPI was different in MBBO subgroups or BMI groups, we conducted multivariate analyses with an interaction term between the duration of diabetes and the groups (MBBO groups or BMI groups). In these analyses, we report the effects of duration and groups and the magnitude of the interaction terms after adjusting for age, sex, and HbA1c. Multivariate analyses were performed for subcohorts stratified by both MBBO and BMI.

To investigate how a trait, characterized by MBBO in this study, might influence the relationship between CPI and the duration of diabetes, we conducted multiple linear regression analysis and estimated this relationship using an approximate equation: CPI = k_0 + k_1 × diabetes duration + k_2 × MBBO, where k_0, k_1, and k_2 are constants. If MBBO did not contribute significantly to the model, the regression lines might be almost

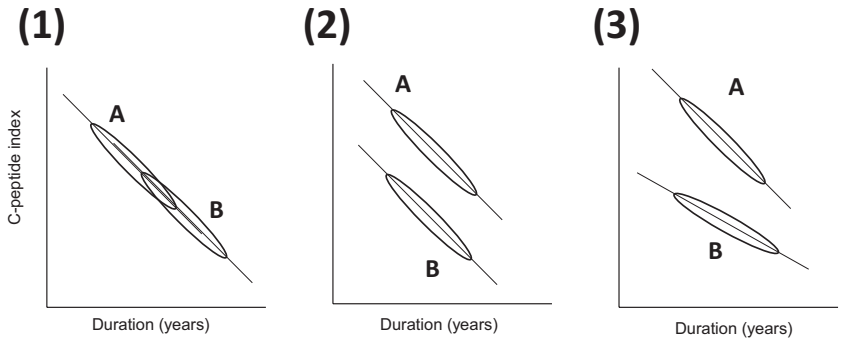

Figure 2. Conceptual figures to show the potential contribution of a variable in a linear regression. Ellipses represent the scatter of data, and lines represent regression lines. (1) Two groups with the same intercept and slope but with different data ranges; (2) two groups with the same slope but different intercepts; and (3) two groups differing in both slope and intercept.

identical (scenario 1) (Fig. 2) (1). When MBBO significantly indicated that the 2 lines were at least different, multiple linear regression analysis including the interaction effect (product of duration of diabetes and MBBO) as a parameter was performed to examine the positional relations of these lines. If MBBO was significant but the interaction effect was not significant, these 2 slopes were not different (scenario 2) (Fig. 2) (2). If MBBO was significant and the interaction effect was also significant, these slopes were different (scenario 3) (Fig. 2) (3).

The significance level in all analyses was $P < .05$, and all statistical analyses were performed with JMP® Pro 13 (SAS Institute, Inc., Cary, NC, US).

3. Results

A. *Clinical characteristics of the study subjects*

The clinical characteristics of the subjects are shown in Table 1. The mean HbA1c was 9.0% (75 mmol/mol), and most of the subjects had poor glycemic control, reflected by the need to be admitted to our hospital. Age at entry and age at type 2 diabetes mellitus diagnosis in patients with MBBO ≥ 30 kg/m^2 were lower than those in the other groups. In the 3 groups, the duration of diabetes was not different, but a higher MBBO value was associated with a higher CPI value. Before admission, 38.8% of subjects were treated with sulfonylurea, 2.7% with glinide, 24.9% with biguanide, 8.3% with thiazolidinedione, 17.3% with α-glucosidase inhibitor, 35.4% with dipeptidyl peptidase-4 inhibitor, 2.4% with sodium glucose cotransporter 2 inhibitor, 4.1% with glucagon-like peptide-1 receptor agonist, 26.3% with insulin, and 21.2% with no medication (Table 1). At the laboratory evaluation, 14.9% of subjects were treated with insulin secretagogues, including sulfonylurea, glinide, dipeptidyl peptidase-4 inhibitor, or glucagon-like peptide-1 receptor agonist, and 45.1% were treated with basal insulin (neutral protamine Hagedorn or long-acting insulin) (Table 1).

B. *Multivariate regression analyses between CPI and various clinical parameters*

To investigate the associations between CPI and other clinical variables, we first performed a univariate analysis between CPI and other variables. This analysis revealed significant associations between CPI and age, sex, age at diagnosis, duration of diabetes, BMI on admission and MBBO (Table 2, univariate analyses). This analysis also revealed an association between CPI and HbA1c at the margin of statistical significance (Table 2, univariate analyses). Baseline variables with P values $< .20$ in the univariate analysis were included in the multivariable models. Age was strongly correlated with age at diagnosis, and age

Table 2. Association between CPI and various variables

	Univariate analyses			Multivariate analysis 1			Multivariate analysis 2		
	Coef	**95%CI**	***P***	**Coef**	**95%CI**	***P***	**Coef**	**95%CI**	***P***
Age	–0.021	–0.027~–0.016	<.0001	–0.011	–0.017~–0.0048	.0005	–0.012	–0.018~–0.0055	.0002
Sex	–0.21	–0.36~–0.048	.011	–0.18	–0.31~–0.038	.013	–0.15	–0.29~–0.014	.031
Age at diagnosis	–0.0076	–0.01~–0.000 15	.015	—	—	—	—	—	—
Duration	–0.028	–0.035~–0.020	<.0001	–0.024	–0.032~–0.016	<.0001	–0.020	–0.027~–0.012	<.0001
Age at MBBO	0.0012	–0.0045~0.0068	.68	—	—	—	—	—	—
HbA1c	–0.039	–0.081~0.0026	.066	–0.097	–0.13~–0.060	<.0001	–0.087	–0.12~–0.049	<.0001
MBBO									
<25	Ref	—	—	—	—	—	—	—	—
≥25,<30	–0.096	–0.26~0.064	.24	0.34	0.15~0.53	.0005			
≥30	0.41	0.26~0.57	<.0001	0.58	0.38~0.78	<.0001			
BMI on admission									
<25	Ref	—	—				Ref	—	—
≥25	0.57	0.43~0.72	<.0001				0.38	0.24~0.53	<.0001

The univariate analyses between CPI and various clinical parameters were evaluated. Baseline variables with *P* values < .20 in the univariate analysis were included in the multivariable models. MBBO was strongly correlated with BMI on admission, so we entered both variables in each model separately to avoid multicollinearity. Multiple linear regressions were used with CPI as the dependent variable and age, sex, HbA1c, duration of diabetes, and MBBO or BMI on admission as independent variables to identify the relationship between CPI and the variables. Multivariate analysis 1 included MBBO. Multivariate analysis 2 included BMI on admission. The threshold for significance was $P < .05$ in the multivariate models.

Abbreviations: BMI, body mass index; MBBO, maximum BMI before onset; CI, confidence interval; Coef, partial regression coefficient; CPI, C-peptide index; Ref, reference.

and age at diagnosis had similar characteristics. We adopted only age in the multiple linear regressions. MBBO was strongly correlated with BMI on admission, so we entered both variables in each model separately to avoid multicollinearity. A multiple linear regression analysis was performed to test the independent association of CPI with MBBO groups and duration of diabetes. This analysis revealed that after adjustment for age, sex, and HbA1c, MBBO groups and duration of diabetes were correlated with CPI (Table 2, multivariate 1). CPI was independently associated with the duration of diabetes and MBBO.

Furthermore, a multiple linear regression analysis was performed to test the independent association of CPI with BMI on admission groups and duration of diabetes. This analysis revealed that after adjustment for age, sex, and HbA1c, BMI on admission groups and duration of diabetes were associated with CPI (Table 2, multivariate analysis 2). CPI was also independently associated with BMI on admission.

C. *CPI correlates with the duration of diabetes in each MBBO group and in each BMI on admission group*

Fig. 3A shows a scattergram and a linear regression analysis of the CPI and duration of diabetes in all subjects. Scattergrams and linear regression analyses of CPI and duration of diabetes in each MBBO group are shown in Fig. 3B (MBBO < 25), Fig. 3C (25 ≤ MBBO < 30), and Fig. 3D (30 ≤ MBBO). CPI was negatively correlated with the duration of diabetes in all 3 groups (MBBO < 25: n = 75, $r = –0.40$, $P = .004$; 25 ≤ MBBO < 30; $n = 164$, $r = –0.40$, $P < .0001$; 30 ≤ MBBO: $n = 171$, $r = –0.43$, $P < .0001$) (Figs. 3B, 3C, and 3D, respectively). In addition, scattergrams and linear regression analyses of CPI and duration of diabetes in each BMI on admission group are shown in Fig. 3E (BMI on admission < 25) and Fig. 3F (25 ≤ BMI on admission). CPI was negatively correlated with the duration of diabetes in the

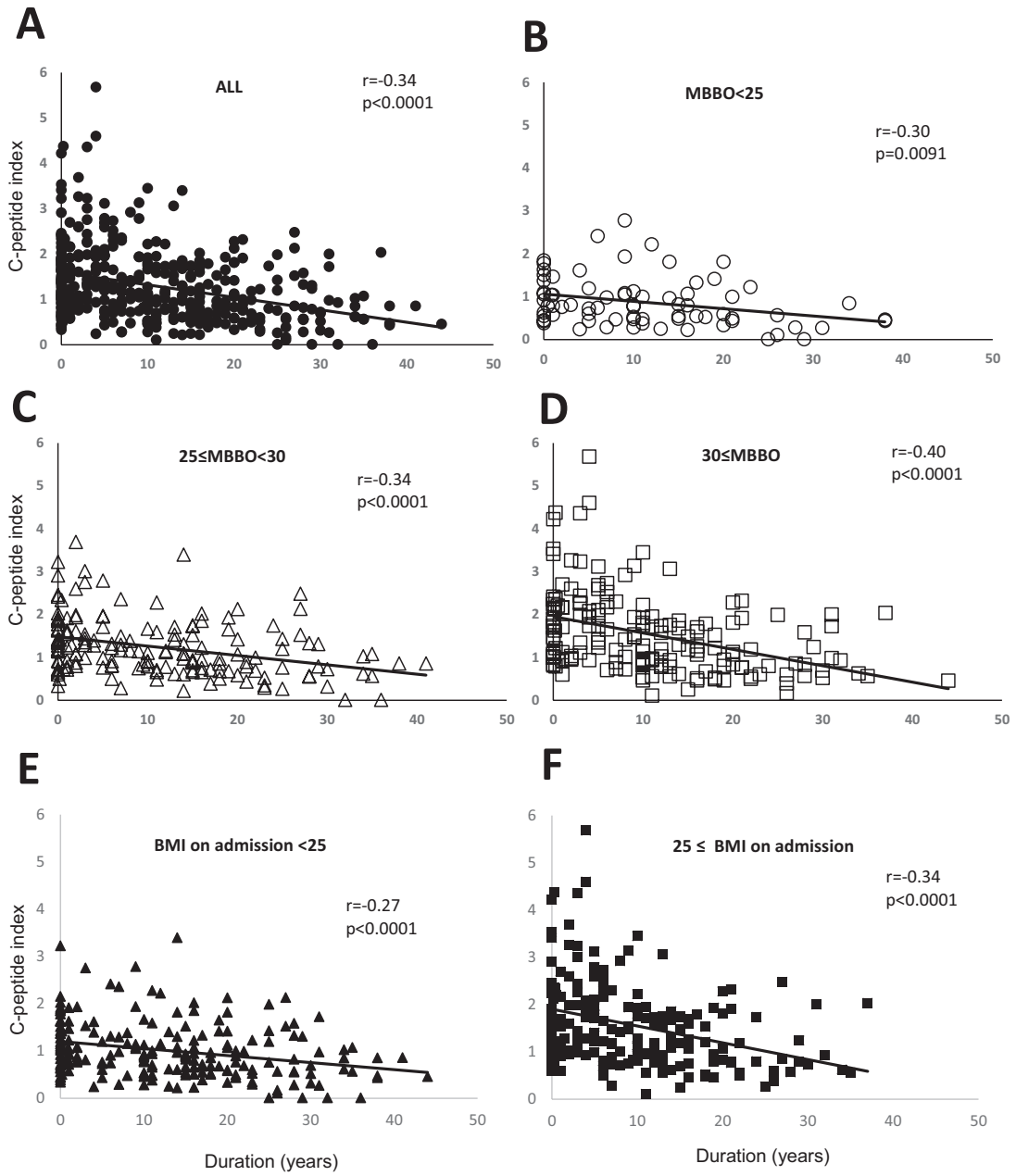

Figure 3. Scattergrams and linear regression analyses between CPI and the duration of diabetes. CPI was negatively correlated with the duration of diabetes in all single analyses. (A) All patients. (B) Patients whose MBBO was less than 25 kg/m^2. (C) Patients whose MBBO was greater than 25 kg/m^2 and less than 30 kg/m^2. (D) Patients whose MBBO was greater than 30 kg/m^2. (E) Patients whose BMI on admission was less than 25 kg/m^2. (F) Patients whose BMI on admission was greater than 25 kg/m^2. MBBO: maximum BMI before onset. Abbreviation: r, partial regression coefficient.

two groups (BMI on admission < 25: $n = 206$, $r = –0.27$, $P < .0001$; 25 ≤ BMI on admission: $n = 204$, $r = –0.34$, $P < .0001$).

D. *The estimated CPIs at diagnosis are different, but the rates of CPI decline are not different in each MBBO group*

To determine the interactions between diabetes duration and MBBO, we performed a multiple linear regression analysis with variables including age, sex, HbA1c, diabetes duration,

Table 3. Interaction effect between duration of diabetes and MBBO or BMI on admission

		Coef	95%CI	*P*
Model 1	Duration	–0.025	–0.033~0.017	<.0001
	MBBO < 25	Ref	–	–
	25 ≤ MBBO < 30	0.34	0.15~0.53	.0005
	30 ≤ MBBO	0.59	0.39~0.79	<.0001
	Duration × "25 ≤ MBBO < 30"	–0.0026	–0.022~0.016	.79
	Duration × "30 ≤ MBBO"	–0.014	–0.034~0.0056	.16
Model 2	Duration	–0.022	–0.030~–0.014	<.0001
	BMI < 25	Ref	–	–
	25 ≤ BMI	0.38	0.23~0.53	<.0001
	Duration × "25 ≤ BMI"	–0.019	–0.033~–0.0049	.0083
Subgroup analyses				
By MBBO groups				
MBBO < 25	Intercept	2.19	1.09~3.30	.0002
	Duration	–0.020	–0.032~–0.0076	.0019
25 ≤ MBBO < 30	Intercept	2.29	1.53~3.05	<.0001
	Duration	–0.026	–0.036~–0.015	<.0001
30 ≤ MBBO	Intercept	3.99	3.09~4.89	<.0001
	Duration	–0.022	–0.038 to –0.0061	.0071
By BMI groups				
BMI < 25	Intercept	2.14	1.48~2.81	<.0001
	Duration	–0.018	–0.025~–0.0097	<.0001
25 ≤ BMI	Intercept	3.65	2.83~4.47	<.0001
	Duration	–0.027	–0.042~–0.013	.0002

Model 1: A multiple linear regression was used with CPI as the dependent variable and duration of diabetes, MBBO and products of duration × MBBO as independent variables, adjusting for age, sex and HbA1c. There was no interaction effect between the duration of diabetes and MBBO. Model 2: A multiple linear regression was used with CPI as the dependent variable, and duration of diabetes, BMI on admission and products of duration × BMI on admission as independent variables, adjusting for age, sex and HbA1c. There was a significant interaction effect between the duration of diabetes and BMI on admission. Subgroup analyses: In each MBBO group, multiple linear regressions were used with CPI as the dependent variable and duration of diabetes as the independent variable adjusting for age, sex and HbA1c. Similar analyses were performed in each BMI group. The threshold for significance was $P < 0.05$.

Abbreviations: BMI, body mass index; Coef: Partial regression coefficient; CI: confidence interval; CPI, C-peptide index; MBBO, maximum BMI before onset; Ref: reference.

MBBO, and the product of diabetes duration and MBBO (Table 3, model 1). The *P* value of this interaction was greater than .05, indicating that the interaction between diabetes duration and MBBO had no significant effect (Table 3, model 1). This fact indicated that the rate of CPI decline was not different among MBBO subgroups after we adjusted CPI for age, sex and HbA1c (Table 3, subgroup analyses by MBBO group). In the analysis performed to test the independent association of CPI with MBBO groups and duration of diabetes, the categorical variables in the MBBO groups were significant (Table 2, multivariate analysis 1). These findings indicated that the estimated CPIs at diagnosis were different but that the rates of CPI decline were not different between the 3 MBBO groups, supporting scenario 2 in Fig. 2 (2).

E. *The estimated CPIs at diagnosis, and the rates of CPI decline are different in each BMI on admission group*

To determine the interactions between diabetes duration and BMI on admission, we performed a multiple linear regression analysis with variables including age, sex, HbA1c, diabetes duration, BMI on admission, and the product of diabetes duration and BMI on admission (Table 3, model 2). The *P* value of this interaction was .0083, indicating that the interaction between diabetes duration and BMI on admission has a significant effect (Table 3, model 2). This result suggested that the rates of CPI decline were different in the BMI on admission subgroups after we adjusted CPI for age, sex, and HbA1c (Table 3, subgroup analyses by BMI group). In the analysis performed to test the independent association of CPI

with BMI on admission groups and duration of diabetes, the categorical variables of the BMI on admission groups were significant (Table 2, multivariate analysis 2). These findings indicated that the estimated CPIs at diagnosis were different and that the rates of CPI decline were also different in the two BMI groups on admission, supporting scenario 3 in Fig. 2 (3).

4. Discussion

This study revealed two new findings. First, the MBBO was independently correlated with CPI and could predict the insulin secretion capacity at diagnosis. Second, MBBO did not seem to affect the rate of CPI decline during treatment for poor glycemic control, while BMI on admission did. Although there have been some reports in which the relationship between BMI and insulin secretion capacity was investigated, this is the first study to clarify the clinical significance of MBBO for predicting beta-cell function.

Some previous reports have shown that the rate of insulin secretion capacity decline was higher in diabetic patients with obesity than in those without obesity (6, 7, 13). Our study also showed similar results in the analysis using BMI on admission. This result suggested that obesity might accelerate the impairment of beta-cell function after diagnosis, probably through the increased load on beta cells due to insulin resistance (14,15), leading to beta-cell apoptosis through oxidative stress, endoplasmic reticulum stress or lipotoxicity (16,17). In contrast, MBBO did not affect the rate of beta-cell function decline in this study. When we performed multiple regression analysis dividing patients into two groups based on MBBO (MBBO ≥ 25 kg/m^2 and MBBO < 25 kg/m^2), we obtained the same results as those obtained in the analysis of BMI on admission (Table 4). These data indicate that MBBO does not affect the rate of beta-cell function decline after the diagnosis of type 2 diabetes mellitus.

In addition, our study revealed that the estimated CPIs at diagnosis were higher in patients who had a higher MBBO. Together with the fact that there was no difference in the rate of CPI decline regardless of the MBBO, we could predict the time when the patient would reach insulin depletion using MBBO. Because this timepoint can be affected by the BMI after diagnosis, it is very important for the preservation of beta-cell function to decrease a patient's BMI during treatment after diagnosis, regardless of the MBBO.

Table 4. Multivariate analyses in two groups divided by MBBO 25 kg/m^2

	Coef	95%CI	*P*
Multivariate analyses 1			
Age	–0.014	–0.02~–0.0082	<.0001
Sex	–0.17	–0.31~–0.027	.020
Duration	–0.022	–0.030~–0.014	<.0001
HbA1c	–0.092	–0.13~–0.055	<.0001
MBBO			
< 25	Ref	–	–
≥25	0.44	0.26~0.62	<.0001
Multivariate analysis 2			
Duration	–0.022	–0.030~–0.014	<.0001
MBBO < 25			
25 ≤ MBBO	Ref	—	—
Duration × "25 ≤ MBBO"	0.0062	–0.012~0.024	.49

We divided patients into two groups based on MBBO (MBBO < 25 kg/m^2 and MBBO≥ 25 kg/m^2). In multivariate analysis 1, multiple linear regressions were used with CPI as the dependent variable and age, sex, HbA1c, duration of diabetes, and MBBO as independent variables. In multivariate analysis 2, multiple linear regressions were used with CPI as the dependent variable and age, sex, HbA1c, duration of diabetes, MBBO, and the product of duration and MBBO as the independent variables. The *P* value of the interaction was 0.49, indicating that the difference in slopes of CPI against duration among MBBO groups was not significant.

Abbreviations: Coef; partial regression coefficient; CI: confidence interval; CPI, C-peptide index; MBBO: maximum BMI before onset; Ref: reference.

Table 5. Multivariate analyses adjusting for medication

	Coef	95%CI	*P*
Model A			
Multivariate analysis 1			
Duration	–0.020	–0.029~–0.012	<.0001
MBBO < 25	Ref	—	—
5 ≤ MBBO < 30	0.33	0.14~0.52	.0007
30 ≤ MBBO	0.56	0.35~0.76	<.0001
Multivariate analysis 2			
Duration	–0.022	–0.031~–0.013	<.0001
MBBO < 25	Ref	—	—
25 ≤ MBBO < 30	0.33	0.14~0.52	.0006
30 ≤ MBBO	0.57	0.36~0.77	<.0001
Duration × "25 ≤ MBBO < 30"	–0.0038	–0.023~0.015	.70
Duration × "30 ≤ MBBO"	–0.016	–0.035~0.0042	.12
Model B			
Multivariate analysis 1			
Duration	–0.025	–0.033~0.017	<.0001
MBBO < 25	Ref	—	—
25 ≤ MBBO < 30	0.33	0.14~0.52	.0006
30 ≤ MBBO	0.59	0.39~0.79	<.0001
Multivariate analysis 2			
Duration	–0.026	–0.034~–0.018	<.0001
MBBO < 25	Ref	—	—
25 ≤ MBBO < 30	0.34	0.15~0.52	.0005
30 ≤ MBBO	0.60	0.40~0.80	<.0001
Duration × "25 ≤ MBBO < 30"	–0.0021	–0.021~0.017	.83
Duration × "30 ≤ MBBO"	–0.014	–0.034~0.0055	.16

Data from multivariate analyses in model A were adjusted for age, sex, HbA1c and medication before admission. Data from multivariate analyses in model B were adjusted for age, sex, HbA1c and medication at evaluation. In multivariate analysis 1, multiple linear regressions were used with CPI as the dependent variable and duration of diabetes and MBBO as independent variables. In multivariate analysis 2, multiple linear regressions were used with CPI as the dependent variable and duration of diabetes, MBBO, and the product of duration and MBBO as independent variables.

Abbreviations: CI: confidence interval; Coef; partial regression coefficient; CPI, C-peptide index MBBO: maximum BMI before onset; Ref: reference.

Hypoglycemic agents might also affect the rate of CPI decline. In fact, thiazolidinedione has been reported to exert a more favorable effect than sulfonylurea on maintaining beta-cell function (18). In this study, various hypoglycemic medicines were used among subjects before admission. Even when we also performed multiple linear regression analysis after adjustment for medications used before admission, CPI proved to be correlated with the duration of diabetes and MBBO independently, and the interaction between diabetes duration and MBBO had no significant effect (Table 5, Model A). Although whether individual hypoglycemic agents might affect the rate of CPI decline could not be evaluated in this study, we found the same correlation between MBBO and CPI independently, regardless of the usage of hypoglycemic agents before admission.

In addition, the measurement of CPI might be affected by the use of insulin secretagogues or basal insulin at evaluation. Even when we performed multiple linear regression analysis after adjustment for the use of these medications at evaluation, CPI was proven to be independently correlated with the duration of diabetes and MBBO, and the interaction between diabetes duration and MBBO had no significant effect (Table 5, Model B). Thus, the same results were obtained regardless of the use of these medications at evaluation, indicating that our conclusion would be the same.

While CPI is obtained from fasting insulin, ΔCPR of glucagon load test is one of the useful and direct indicator for dynamic insulin secretion capacity (19). In our previous study, relative beta cell area was correlated with both CPI and ΔCPR (11). Glucagon load test was

Table 6. Interaction effect between duration of diabetes and MBBO or BMI on admission in 299 Patients who received glucagon load test

	Coef	95%CI	*P*
Model 1			
Duration	–0.041	–0.055~ 0.026	<.0001
MBBO < 25	Ref	—	—
25 ≤ MBBO < 30	0.64	0.28~1.01	.0006
30 ≤ MBBO	0.78	0.39~1.16	<.0001
Duration × "25 ≤ MBBO < 30"	–0.026	–0.063~0.011	.17
Duration × "30 ≤ MBBO"	–0.040	–0.078~ 0.0018	.040
Model 2			
Duration	–0.039	–0.054~–0.025	<.0001
BMI < 25	Ref	—	—
25 ≤ BMI	0.57	0.29~0.85	<.0001
Duration × "25 ≤ BMI"	–0.042	–0.068~–0.015	.0024
Subgroup analyses			
By MBBO groups			
MBBO < 25			
Intercept	0.99	–0.42~2.40	.17
Duration	–0.016	–0.040~0.0078	.18
25 ≤ MBBO < 30			
Intercept	3.21	2.03~4.39	<.0001
Duration	–0.038	–0.060~–0.015	.011
30 ≤ MBBO			
Intercept	3.30	2.30~4.31	<.0001
Duration	–0.052	–0.081~–0.023	.0005
By BMI groups			
BMI < 25			
Intercept	2.01	1.14~2.88	<.0001
Duration	–0.021	–0.036~–0.0055	.0077
25 ≤ BMI			
Intercept	3.45	2.50~4.39	<.0001
Duration	–0.061	–0.088~–0.033	<.0001

Model 1: A multiple linear regression was used with ΔCPR as the dependent variable and duration of diabetes, MBBO and products of duration × MBBO as independent variables, adjusting for age, sex and HbA1c. There was no interaction effect between the duration of diabetes and MBBO. Model 2: A multiple linear regression was used with ΔCPR as the dependent variable, and duration of diabetes, BMI on admission and products of duration × BMI on admission as independent variables, adjusting for age, sex and HbA1c. There was a significant interaction effect between the duration of diabetes and BMI on admission. Subgroup analyses: In each MBBO group, multiple linear regressions were used with CPI as the dependent variable and duration of diabetes as the independent variable adjusting for age, sex and HbA1c. Similar analyses were performed in each BMI group. The threshold for significance was $P < .05$.

Abbreviations: BMI, body mass index; CI, confidence interval; Coef: Partial regression coefficient; CPI, C-peptide index; Ref: reference.

performed in 299 patients of 410 patients in our study, and ΔCPR was defined as increment in serum CPR level at 6 minutes after intravenous injection of 1 mg glucagon. To evaluate whether CPI is a reliable indicator of beta cell function, we confirmed a correlation of CPI and ΔCPR. In 299 patients with glucagon load test, CPI was strongly correlated with ΔCPR ($r = 0.62$, $P < .0001$). We divided these participants into 3 groups (low group: MBBO < 25; $n = 57$, intermediate group: 25 ≤ MBBO < 30; $n = 119$, high group: 30 ≤ MBBO; $n = 123$). We also divided participants into 2 groups: one was BMI < 25, and the other was 25 ≤ BMI. In 299 patients, mean ages was 62 ± 14 years. Mean diabetes duration was 11 ± 10 years, and there was no difference in duration among these three MBBO groups. In each MBBO group, CPI was 0.58 in low group, 1.0 in intermediate group, and 1.2 in high group. ΔCPR was 1.2 ng/ml in low group, 1.7 ng/mL in middle group, and 1.9 ng/mL in high group. We performed multiple linear regressions for ΔCPR as a dependent variable and obtained almost the same results. A multiple linear regression analysis using MBBO revealed an

interaction effect between the low MBBO group and the high MBBO group (Table 6, Model 1). When we paid attention to the rate of ΔCPR decline, there was no difference among the three groups. In subgroup analyses, multiple linear regressions adjusting for age and sex indicated an annual decline rate of ΔCPR as the coefficient of duration/intercept in each group (Table 6, subgroup analyses by MBBO group). The decline rate of the low MBBO group was 1.6%, that of the intermediate MBBO group was 1.2%, and that of the high MBBO group was 1.6%. Furthermore, we performed a multiple linear regression analysis using BMI on admission instead of MBBO. The *P* value of this interaction was .0024, indicating that the interaction between diabetes duration and BMI on admission had a significant effect (Table 6, Model 2). The decline rate of the low BMI group was 1.0%, and that of the high BMI group was 1.8%, suggesting that the decline rates of ΔCPR were different in the BMI on admission subgroups (Table 6, subgroup analyses by BMI group). These analyses and strong correlation between CPI and ΔCPR revealed the usefulness of CPI for evaluating insulin production capacity.

This study had some limitations. First, it was a retrospective cross-sectional observational study. Prospective longitudinal studies with evaluation of the effects of treatments are necessary to clarify the actual change in individual patients' CPIs. Second, we excluded patients whose maximum BMI was reached after the diagnosis of type 2 diabetes mellitus from this study. Because it is conceivable that a high BMI after diagnosis will accelerate the impairment of beta-cell function, the rate of CPI decline would be higher in each group divided by MBBO if we included patients who reached their maximum BMI after diagnosis. Further study is needed to clarify this issue. Third, we struggled to control patients' glucose level in their hospital, but a part of patients did not had good control. This fact was one of our study limitations.

In conclusion, MBBO is a factor that is independently correlated with beta-cell function, may estimate insulin secretion capacity at onset, and may possibly predict a patient's insulin secretion capacity under appropriate health control. In addition, MBBO does not affect the rate of insulin secretion capacity decline, although BMI on admission for treatment of poor glycemic control does. It is important for the preservation of beta-cell function to decrease a patient's BMI during treatment, regardless of the MBBO.

Acknowledgments

Financial Support: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author Contributions: HO, KF, and HI designed the whole project and wrote the manuscript. HO contributed to the acquisition and analysis of the data. YH and YF assisted with the data analysis and reviewed and edited the manuscript. TK and JK assisted with the study design and reviewed and edited the manuscript. AT reviewed and edited the manuscript. SK provided statistical advice regarding the study design and assisted with the data analysis. IS assisted with the study design and analysis and reviewed and edited the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final version of the manuscript. Kenji Fukui is the guarantor of this work.

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Disclosure Summary: No potential conflicts of interest relevant to this article were reported, and the authors have nothing to disclose.

Data availability: The data sets generated and analyzed in the current study are not publicly available but are available from the corresponding author on reasonable request.

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