Utility of indices using C-peptide levels for indication of insulin therapy to achieve good glycemic control in Japanese patients with type 2 diabetes

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ABSTRACT

Aims/Introduction: Type 2 diabetes is progressive in that therapy must be altered over time, which is partly as a result of the progressive loss of pancreatic β-cell function. To elucidate the relationship between residual endogenous insulin secretion and the necessity of insulin therapy to achieve good glycemic control, indices using serum C-peptide immunoreactivity (CPR) were analyzed in patients with type 2 diabetes.

Materials and Methods: The data of 201 Japanese patients with type 2 diabetes who achieved the target of glycemic control during admission were analyzed retrospectively. Indices using CPR including fasting CPR (FCPR), CPR 6 min after intravenous injection of glucagon (CPR-6 min), increment of CPR (ΔCPR), secretory unit of islet in transplantation index (SUIT) and C-peptide index (CPI) were compared between the group requiring insulin (insulin group) and the group not requiring insulin (non-insulin group). A receiver–operator characteristic (ROC) curve was made, and optimal cut-off point and likelihood ratio were determined for each index.

Results: All indices of CPR were lower in the insulin group compared with those in the non-insulin group. Likelihood ratios at the optimal point of FCPR, CPR-6 min, ΔCPR, SUIT, and CPI were 2.0, 2.1, 1.6, 2.3 and 2.8, respectively. Optimal cut-off point of CPI was 1.1 ng/mg. Sensitivity and specificity at optimal point of CPI were 61 and 78%, respectively.

Conclusions: The advantage of CPI of the indices of CPR to select insulin therapy to achieve good glycemic control was shown, but limitations of the predictive abilities of the indices using CPR should be taken into account. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2010.00096.x, 2011)

KEY WORDS: C-peptide, Insulin therapy, Glycemic control

INTRODUCTION

Type 2 diabetes is a heterogeneous disease characterized by insulin resistance and defective insulin secretion[1], and is progressive in that therapy must be altered over time. Initially on diagnosis, diet and exercise are generally adequate to achieve good glycemic control; oral hypoglycemic agents (OHA) are required later, when patients cannot achieve control with diet and exercise alone. Daily insulin injection is indicated when patients are unable to achieve control with a combination of oral agents, diet and exercise[2,3]. Insulin therapy is required in these patients not for survival, as is found in type 1 diabetes, but for good glycemic control[4]. This requirement is, at least in part, as a result of the progressive loss of pancreatic β-cell function. The results of the United Kingdom Progressive Diabetes Study (UKPDS) shows that pancreatic β-cell function (%β), assessed by Homeostasis Model Assessment (HOMA) in patients allocated to diet or OHA, decreased approximately 25% in 5 years[5]. A decline in endogenous insulin secretion over more than several decades of diabetes was observed in a cross-sectional study[6].

Determination of fasting serum C-peptide level and stimulated serum C-peptide level by intravenous glucagon is used widely to assess endogenous insulin secretory reserves[7–10]. There are several reports regarding the correlation between levels of residual endogenous insulin secretion and the choice of insulin therapy to achieve glycemic control[11–14]. However, in these studies, because the glycemic goal was not described clearly or was inappropriate, patients with insufficient glycemic control by the selected mode of therapy were sometimes included.

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In the present study, to evaluate the clinical significance of measures of serum C-peptide in achieving good glycemic control, we retrospectively analyzed the use of indices of endogenous insulin secretion in type 2 diabetes patients admitted to our hospital. Using data of patients who achieved the target of glycemic control during the period of admission, the patients were divided into two groups: one that achieved good control without the use of insulin (non-insulin group) and the other that required the use of insulin (insulin group), and the indices using serum C-peptide were compared between them. Optimal values and the utility of indices using serum C-peptide to select insulin therapy to achieve good glycemic control were analyzed.

MATERIALS AND METHODS

Subjects

A total of 746 Japanese patients with type 2 diabetes admitted between 2003 and 2009 to Kyoto University Hospital for poor glycemic control were enrolled in the present study. Type 2 diabetes mellitus was diagnosed based on the criteria of the American Diabetes Association (ADA)[15]. As indicated in Figure S1, 76 patients including those with pancreatic disease and liver disease, those taking diabetogenic medication and pregnant women were excluded. A total of 40 patients with incomplete clinical examinations also were excluded, and 66 patients with serum creatinine ≥1.3 mg/dL were excluded, as serum C-peptide immunoreactivity (CPR) is elevated by decreased renal function[16]. The data of 90 patients taking oral hypoglycemic agents (OHA) plus insulin at discharge were excluded. Good control was defined as mean preprandial capillary plasma glucose level <130 mg/dL, according to the glycemic control recommendation of ADA[17]. The 474 patients were divided into two groups: 201 patients who achieved good glycemic control (achieved group) and 273 patients who did not (non-achieved group). As shown in Figure S2, of the 201 patients in the achieved group, 47, 107, 38 and nine patients were treated with diet alone, OHA, insulin and insulin plus OHA at admission, respectively. At discharge, 24, 95 and 82 patients were treated with diet alone, OHA and insulin, respectively. Patients treated with diet alone and OHA at discharge comprised the non-insulin group; patients treated with insulin at discharge comprised the insulin group. A total of 166 patients of the 474 patients in the achieved or non-achieved group at discharge who could be confirmed within 6 months after discharge to achieve <7.4% in HbA_{1c}, which excludes 'not good' and 'poor' for assessment of glycemic control in the treatment guide for diabetes of the Japan Diabetes Society (JDS guide)[18], were re-analyzed to determine the cut-off point for C-peptide index (CPI) for longer duration of glycemic control. Of the 201 patients in the achieved group at discharge, 85 were excluded as a result of readmission or alteration to the mode of therapy, or were not followed as outpatients due to a change of hospital. Of the remaining 116 patients, 90 showed <7.4% HbA_{1c} within 6 months after discharge. Of the 273 patients in the non-achieved group at discharge, 137 were excluded as a result of readmission or alteration to the mode of therapy, or were not followed as outpatients due to a change of hospital. In the remaining 136 patients, 76 achieved <7.4% HbA_{1c} within 6 months after discharge. In these 166 patients, analysis of optimal values and the utility of CPI during admission was carried out.

Methods

On the first day in hospital, medical history, physical examination and laboratory evaluation including glycosylated hemoglobin were carried out. HbA_{1c} was measured using HPLC (HA-8180; Arcray, Kyoto, Japan). The HbA_{1c} (%) value was estimated as an National Glycohemoglobin Standardization Program equivalent (%) calculated by the formula: HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%, considering the relational expression of HbA_{1c} (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (National Glycohemoglobin Standardization Program)[19]. β-cell function was evaluated within 1 week after overnight fast by glucagon test measuring CPR before (fasting CPR [FCPR]) and 6 min after i.v. injection of 1 mg glucagon (CPR-6 min)[7], as this test is valid in patients taking insulin therapy. Increment of CPR (ΔCPR) was obtained by subtracting FCPR from CPR-6 min. SUIT index (SUIT) (%) was calculated by the formula: 1500 × FCPR (ng/mL)/(fasting plasma glucose [FPG; mg/dL] − 61.7)[20]. CPI (ng/mg) was calculated by the formula: 100 × FCPR (ng/mL)/FPG (mg/dL). Serum CPR was measured by immunoenzymometric assay (EIA; ST AIA-PACK C-Peptide, Toso corporation, Tokyo, Japan). In patients taking OHA, medication was stopped for the glucagon test, but was maintained until 1 day before to prevent hyperglycemia during the test[6]. Fasting plasma glucose was measured by the glucose oxidase method when the glucagon test was carried out. Patients were treated according to the JDS guide[18]. Treatment policy including diet therapy, exercise therapy, pharmacotherapy and education for each patient was determined by Japanese Board Certified Diabetologists certified by the Japan Diabetes Society. Patients took medical nutritional therapy (25–30 kcal/kg of standard bodyweight/day consisting of 58% carbohydrate, 18% protein and 24% fat energy intake percentages) with counseling by a registered dietitian. Preprandial capillary plasma glucose levels were monitored three t.i.d. during hospitalization. The study protocol was approved by the ethics committee of Kyoto University.

Statistical analysis

Statistical analysis was carried out with the Stat View 5.0 system (SAS institute, Cary, NC, USA). Data are presented as mean ± SE unless otherwise stated. Clinical parameters among the two groups were compared by Mann–Whitney *U*-test. *P*-values <0.01 were considered statistically significant. Histograms and receiver–operator characteristic (ROC) curve were made for FCPR, CPR-6 min, ΔCPR, SUIT and CPI respectively, and sensitivity, specificity, cut-off values, area under the ROC curve (AUC) and the likelihood ratio were calculated.

RESULTS

Clinical profiles of patients with mean preprandial capillary plasma glucose levels at discharge of <130 mg/dL (achieved group) and ≥130 mg/dL (non-achieved group), respectively, are shown in Table 1. Patients of the non-achieved group were older, had lower body mass index at admission, higher mean preprandial capillary plasma glucose level both at admission and at discharge, longer years from diagnosis and lower endogenous insulin secretion indices than those of the achieved group. The clinical stages of diabetic nephropathy and retinopathy were more progressed in the non-achieved group than those in the achieved group. The relationships between indices using serum C-peptide and selected modes of therapy at discharge were analyzed based on the data of the achieved group.

The clinical profiles of patients not requiring insulin for good glycemic control (non-insulin group) and those requiring insulin (insulin group) are shown in Table 2. The patients of the insulin group were older, has lower body mass index, higher HbA_{1c} at admission, higher mean preprandial capillary plasma glucose level at admission, longer years from diagnosis and lower endogenous insulin secretion indices compared with those of the non-insulin group. As shown in Figure S2, the mode of therapy in 41 patients was altered from diet alone or OHA to insulin during admission. The average number of hospital days before altering the therapeutic mode of these patients was 3.1 ± 3.4 (mean ± SD). The reasons for the change to insulin therapy were the necessity of tight glycemic control before operation in five patients, marked hyperglycemia (a fasting plasma glucose level of 250 mg/dL or above, or a causal plasma glucose of 350 mg/dL or above)[21] or both the presence of hyperglycemia and ketosis in 11 patients, and persistent hyperglycemia with OHA in 25 patients. HbA_{1c} at admission of these patients was 10.2 ± 2.2% (mean ± SD). In five patients, the mode of therapy was altered from insulin to OHA. The average number of hospital days before this change was 7.6 ± 4.3 (mean ± SD); the reason was improved glycemic control despite a decrease in the required dosage of insulin. HbA_{1c} at admission of these patients was 10.1 ± 4.4% (mean ± SD). Another patient treated with OHA plus insulin at admission was changed to OHA alone after nine hospital days because of improved glycemic control. Of the 113 patients with therapy of diet alone or OHA both at admission and at discharge, 19 transiently used insulin during the period of admission.

The category of OHA at discharge is shown in Table S1a. In 95 patients treated with OHA, 60 and 29 patients were prescribed sulfonylurea alone or in combination, and biguanide alone or in combination, respectively. In the insulin group, 50 of 86 patients were given premixed insulin b.i.d. at discharge. As shown in Table S1b, the prescribed daily dosages of gliclazide, glimepiride and metformin required were <80, 4 and 750 mg,

Table 1 | Clinical profiles of patients who achieved good glycemic control

	Achieved	Non-achieved	*P*
No. subjects	201	273	
Duration of hospitalization (days)	22.0 ± 0.7	23.6 ± 0.7	0.1115
Age (years)	60.2 ± 0.9	64.5 ± 0.7*	0.0002
Male/female	127/74	159/114	
Systolic blood pressure (mmHg)	124.5 ± 1.0	126.9 ± 1.1	0.1076
Diastolic blood pressure (mmHg)	74.6 ± 0.7	73.6 ± 0.6	0.2653
BMI (kg/m^2)	25.2 ± 0.3	23.8 ± 0.3*	0.0005
HbA_{1c} at admission (%)	9.5 ± 0.1	9.8 ± 0.1	0.0776
PG at admission (mg/dL)	181.1 ± 4.7	209.5 ± 3.9*	<0.0001
PG at discharge (mg/dL)	112.2 ± 0.9	163.2 ± 1.9*	<0.0001
Years from diagnosis	9.1 ± 0.6	13.5 ± 0.6*	<0.0001
FCPR (ng/mL)	1.87 ± 0.06	1.65 ± 0.05*	0.0054
CPR-6 min (ng/mL)	3.99 ± 0.14	3.41 ± 0.10*	0.0006
ΔCPR (ng/mL)	2.12 ± 0.09	1.76 ± 0.07*	0.0011
SUIT (%)	40.6 ± 1.9	32.4 ± 2.0*	0.0043
CPI (ng/mg)	1.34 ± 0.05	1.09 ± 0.04*	<0.0001
Clinical stage of nephropathy (normal/microalbuminuria/macroalbuminuria)	129/56/16 (64/28/8)	133/80/60 (49/29/22)	
Clinical stage of retinopathy (NDR/mild NPDR/moderate NPDR/severe NPDR/PDR)	141/25/26/4/5 (71/12/13/2/2)	112/53/45/22/41 (41/20/16/8/15)	

Data are presented as mean ± SE. *P < 0.01 versus achieved. Achieved group: mean preprandial capillary plasma glucose levels at discharge <130 mg/dL compared with those who did not achieve good glycemic control (non-achieved group ≥130 mg/dL). BMI, body mass index; CPI, C-peptide index; **Δ**CPR, increment of C-peptide immunoreactivity; CPR-6 min, C-peptide immunoreactivity 6 min after intravenous injection of glucagon; FCPR, fasting C-peptide immunoreactivity; NDR, no diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PG, mean preprandial capillary plasma glucose level; SUIT, secretory unit of islet in transplantation index. Numbers in parentheses indicate percentages.

Table 2 | Clinical profiles of patients who achieved good glycemic control without requiring the use of insulin and those requiring insulin to achieve good glycemic control

	Non-insulin	Insulin	*P*
No. subjects	119	82	
Male/female	82/37	45/37	
Age (years)	58.4 ± 1.1	62.9 ± 1.3*	0.0099
Systolic blood pressure (mmHg)	124.4 ± 1.4	126.4 ± 1.7	0.3598
Diastolic blood pressure (mmHg)	77.3 ± 1.0	73.3 ± 1.3	0.0135
BMI (kg/m^2)	26.0 ± 0.4	24.0 ± 0.4*	0.0019
HbA_{1c} at admission (%)	9.2 ± 0.2	10.0 ± 0.2*	0.0050
PG at admission (mg/dL)	163.2 ± 5.0	206.9 ± 8.0*	<0.0001
PG at discharge (mg/dL)	110.9 ± 1.2	114.2 ± 1.3	0.0602
Years from diagnosis	7.8 ± 0.6	10.9 ± 1.0*	0.0052
FCPR (ng/mL)	2.06 ± 0.07	1.61 ± 0.09*	0.0001
CPR-6 min (ng/mL)	4.48 ± 0.18	3.29 ± 0.19*	<0.0001
ΔCPR (ng/mL)	2.43 ± 0.12	1.68 ± 0.12*	<0.0001
SUIT (%)	47.2 ± 2.5	31.1 ± 2.7*	<0.0001
CPI (ng/mg)	1.57 ± 0.07	1.06 ± 0.06*	<0.0001

Data are presented as mean ± SE. *P < 0.01 versus non-insulin. Good glycemic control: mean preprandial capillary plasma glucose levels at discharge <130 mg/dL.
BMI, body mass index; CPI, C-peptide index; ΔCPR, increment of C-peptide immunoreactivity; CPR-6 min, C-peptide immunoreactivity 6 min after intravenous injection of glucagon; FCPR, fasting C-peptide immunoreactivity; PG, mean preprandial capillary plasma glucose level; SUIT, secretory unit of islet in transplantation index.

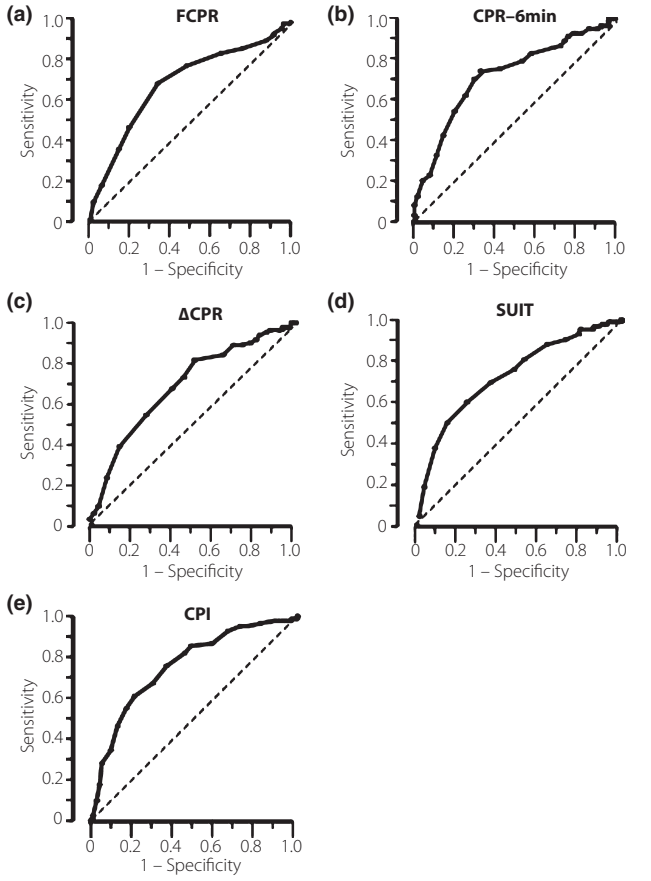

Figure 1 | Receiver–operator characteristic curves of (a) fasting C-peptide immunoreactivity (FCPR), (b) CPR 6 min after intravenous injection of glucagon (CPR-6 min), (c) increment of CPR (ΔCPR), (d) secretory unit of islet in transplantation index (SUIT) and (e) C-peptide index (CPI) of patients with mean preprandial capillary plasma glucose levels of <130 mg/dL at discharge.

respectively in almost all (more than 95%) patients. Daily insulin dosage was 22.0 ± 11.1 U (mean ± SD) in the insulin group.

In Figure S3, peak relative frequency of indices using CPR of patients with mean preprandial capillary plasma glucose levels of <130 mg/dL at discharge in the insulin group and the non-insulin group, respectively, is shown (FCPR: 1.50–1.75, 2.00–2.25 ng/mL; CPR-6 min: 2.75–3.00, 4.00–4.25 ng/mL; ΔCPR: 1.25–1.50, 1.25–1.50 plus 2.25–2.50 ng/mL; SUIT: 15–20, 25–30 plus 35–40 plus 45–50%; and CPI: 0.8–0.9, 1.5–1.6 ng/mg). According to ROC curves of indices using CPR shown in Figure 1, AUC, cut-off values and values at optimal cut-off points including sensitivity, specificity and the likelihood ratio were determined and shown in Table 3. CPI is the most relevant of these indices for selecting insulin therapy to achieve good glycemic control, because the likelihood ratio and AUC of CPI is greatest.

The ROC curve of CPI of patients who achieved <7.4% HbA_{1c} within 6 months after discharge is shown in Figure 2. According to ROC curves of CPI in Figure 2, the AUC (0.75), cut-off values (optimal: 1.2; 90% specificity 0.8; 90% sensitivity 1.7 ng/mg), and values at optimal cut-off points including sensitivity (73%), specificity (71%) and the likelihood ratio (2.5) were determined.

DISCUSSION

Medical nutritional therapy (MNT) improves glycemic control in patients with type 2 diabetes regardless of their modes of therapy including diet alone, OHA and insulin[22–24]. Diet therapy is the basis and starting point of treatment of all patients with diabetes[25], and failure of diet therapy alone might predict the inability to attain optimal glycemic control by any of these modes of therapy. To precisely analyze the relationship between endogenous insulin secretion and the appropriate mode of therapy for achieving good glycemic control, we used data of hospitalized patients under optimal therapy including proper MNT. Thus, our results are more likely to be valid in patients with appropriate care behaviors. Although inappropriate care behavior is an obstacle to achieving good glycemic control over a longer duration, our results suggest a basis for beginning insulin therapy in patients who do not achieve good glycemic control with diet alone or OHA despite the practice of appropriate care behavior.

Table 3 | Analysis of indices using serum C-peptide of patients with mean preprandial capillary plasma glucose levels of <130 mg/dL at discharge

	FCPR	CPR-6 min	ΔCPR	SUIT	CPI
AUC	0.69	0.71	0.69	0.72	0.75
Cut-off values	(ng/mL)	(ng/mL)	(ng/mL)	(%)	(ng/mg)
Optimal	1.75	3.75	2.25	30	1.1
90% Specificity	1.00	2.25	1.00	20	0.7
90% Sensitivity	2.75	5.25	3.25	55	1.7
Values at optimal cut-off points					
Sensitivity (%)	70	74	82	61	61
Specificity (%)	66	65	49	73	78
Likelihood ratio	2.0	2.1	1.6	2.3	2.8

AUC, area under receiver–operator characteristics curve; CPI, C-peptide index; ΔCPR, increment of C-peptide immunoreactivity; CPR-6 min, C-peptide immunoreactivity 6 min after intravenous injection of glucagon; FCPR, fasting C-peptide immunoreactivity; SUIT, secretory unit of islet in transplantation index

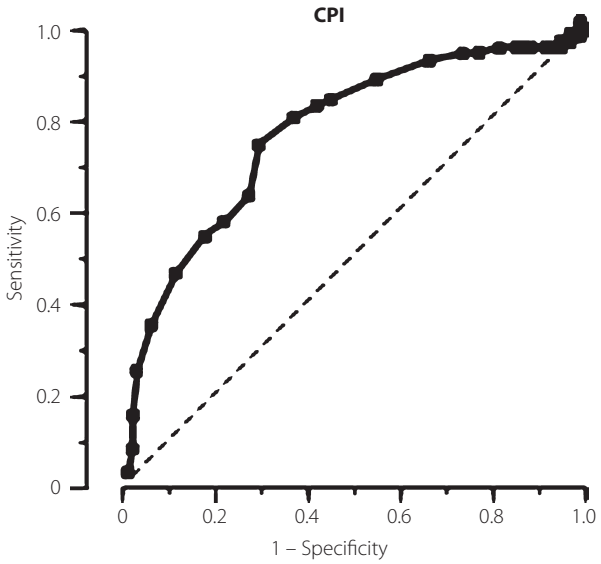

Figure 2 | Receiver–operator characteristic curve of C-peptide index (CPI) of patients who achieved <7.4% HbA_{1c} within 6 months after discharge.

In the present study, just 42% of patients achieved good control during hospital admission, partly because the aim of admission was not necessarily to achieve good control during the period of admission, but to establish a treatment policy for the achievement of good control after discharge. The percentage of patients treated with insulin at discharge was higher in the non-achieved group than in the achieved group (non-achieved group: 67%; achieved group: 41%). Of the patients treated with OHA at admission in the achieved group, 39% had therapy changed to insulin, whereas 73% of the patients treated with OHA at admission in the non-achieved group had therapy changed to insulin. These results might indicate more intensive therapy in the case of the non-achieved group. Of the 136 patients in the non-achieved group at discharge, 76 showed <7.4% HbA_{1c} within 6 months after discharge, showing fair glycemic control in some of the patients of this group over the longer term. As shown in Table 1, the non-achieved group had more progressive diabetic complications and more years from diagnosis compared with the achieved group. These factors might prompt therapy that aims at a more gradual improvement of glycemic control to prevent hypoglycemia. In addition, the non-achieved group showed higher glycemic levels at admission than that of the achieved group, whereas the duration of hospitalization was similar.

Although there have been several reports regarding the utility of indices of endogenous insulin secretion to indicate initiation of insulin therapy to improve glycemic control[11–14], none has compared the utility of the various indices. In the present study, as shown by the likelihood ratio and by AUC, CPI is shown to be the most useful among the five indices.

CPI was used as an index of endogenous insulin secretion in several reports[26–28], but its advantage over other indices and the scientific basis was unclear. The SUIT index (SUIT) was developed using FCPR and plasma glucose level after islet transplantation[19]. The linear relationship between FCPR and FPG in individual subjects shows a plasma glucose level (61.7 mg/dL) assumed to suppress C-peptide to zero. Transplantation of islets from non-diabetic donors increases the slope (FCPR/[FPG − 61.7]), suggesting an index of transplanted β-cell mass. Although a correlation between SUIT and CPR 6 min after intravenous injection of 1 mg glucagon (CPR-6 min) is observed in type 2 diabetes ($r = 0.58$), it is weaker than that in patients after islet transplantation ($r = 0.82$)[19].

Autopsy reveals that β-cell mass is decreased in patients with type 2 diabetes compared with that in healthy subjects[29–31]. Recently, in 33 subjects at various stages of glucose tolerance, a correlation between β-cell areas of a sample obtained during pancreatectomy, and serum levels of CPR and insulin before the operation was analyzed[32]. Interestingly, β-cell areas are positively correlated with fasting insulin/FPG ($r = 0.51$, $P = 0.0024$) and FCPR/FPG ($r = 0.63$, $P < 0.0001$), but are not significantly

correlated with homeostasis model assessment β-cell function (HOMA-β). Because SUIT resembles HOMA-β in that insulin secretion is assumed to be suppressed to zero at approximately 60 mg/dL glucose in the formula, CPI might be a better index of residual β-cell mass than SUIT in subjects with glucose intolerance. Furthermore, CPI is not affected by exogenous insulin[27], which might favor reproducibility of the results in patients with insulin therapy. Determination of the index using a one-point blood sample without the use of loading agents also favors CPI.

In results derived from CPI of patients with mean preprandial capillary plasma glucose levels of <130 mg/dL at discharge, AUC was 0.75, optimal cut-off value was 1.1 ng/mg with 61% sensitivity and 78% specificity, and values at 90% sensitivity and at 90% specificity were 1.7 and 0.7 ng/mg, respectively. Interestingly, in results derived from CPI of patients who achieved <7.4% HbA_{1c} within 6 months after discharge, AUC was 0.75, optimal cut-off value was 1.2 ng/mg with 73% sensitivity and 71% specificity, and values at 90% sensitivity and at 90% specificity were 1.7 and 0.8 ng/mg, respectively, similar to the values evaluated by mean preprandial glucose levels at discharge. These values are also similar to those in a previous report in Japanese using the data of 180 subjects from another institution (optimal cut-off value: 1.0 with 62% sensitivity and 81% specificity; values at 90% sensitivity: 1.8; 90% specificity: 0.7 ng/mg), although good glycemic control was defined as 8.4% in HbA_{1c}, which is somewhat inadequate[14]. Thus, CPI might be a predictor of suitable therapy to achieve fair glycemic control not only for the short-term, but also for longer duration.

The main limitation of the present study is that it is a retrospective analysis of inpatients at one hospital, and the protocol for starting insulin therapy was not defined precisely. However, in the achieved group analyzed as subjects, the decisions as to whether to start insulin therapy made by Japanese Board Certified Diabetologists were confirmed retrospectively to have been made according to the treatment guide for diabetes of the Japan Diabetes Society, as discussed in the results section.

In conclusion, we have shown the advantage of CPI of indices using CPR to select insulin therapy to achieve good glycemic control. However, limitations of the predictive abilities of indices using CPR generally and the importance of observation of the clinical therapeutic course must be taken into consideration.

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The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Process of selection of subjects for analysis.
Figure S2 | Therapeutic modes of analyzed patients at admission and discharge, and the required alteration of therapy during the period of admission.
Figure S3 | Relative frequency distribution of C-peptide indices of patients with mean preprandial capillary plasma glucose levels of <130 mg/dL at discharge in the non-insulin and insulin group.
Table S1 | Details of medication and daily dosages of oral hypoglycemic agents used at discharge

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