

Secretory units of islets in transplantation index is a useful predictor of insulin requirement in Japanese type 2 diabetic patients

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Keywords

Insulin requirement, Type 2 diabetes, β -cell function

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J Diabetes Invest 2014; 5: 570–580

doi: 10.1111/jdi.12181

ABSTRACT

Aims/Introduction: The objective of the present study was to clarify the validity of β -cell function-related parameters for predicting the insulin requirement of Japanese type 2 diabetic patients.

Materials and Methods: In 188 patients with type 2 diabetes who had been admitted to the University of Toyama Hospital (Toyama, Japan) without receiving insulin therapy, we carried out a cross-sectional study examining the relationship between the homeostasis model assessment of β -cell function (HOMA- β) and C-peptide-based indices, and also carried out a retrospective study to examine the utility for predicting insulin requirement of several β -cell function-related indices using a receiver operating characteristic (ROC) curve analysis.

Results: The secretory units of islets in transplantation index (SUIT) had the strongest correlation with HOMA- β , followed by the fasting serum C-peptide immunoreactivity index (CPI); the fasting serum C-peptide immunoreactivity itself (F-CPR) had the least correlation. The CPI, HOMA- β and SUIT were significantly lower in the insulin-requiring group than in the non-insulin-requiring group, even after adjustments for confounding factors ($P < 0.01$). The areas under the ROC curve for insulin requirement were 0.622, 0.774, 0.808, and 0.759 for F-CPR, CPI, SUIT, and HOMA- β , respectively. The cut-off values of SUIT, CPI, and HOMA- β for an over 80% specificity for the prediction of insulin therapy were 23.5, 1.00, and 14.9, respectively.

Conclusions: The present study shows that SUIT is the best predictor of insulin requirement among these β -cell function-related markers.

INTRODUCTION

Type 2 diabetes is a progressive disease, and pancreatic β -cell function might have a crucial role during the course of its progression^{1,2}. Indeed, the results of the United Kingdom Progressive Disease Study showed that a deterioration in glycemic control observed over time was related to the decline in β -cell function, as assessed using modeled plasma insulin/glucose

(homeostasis model assessment of β -cell function [HOMA- β]) in patients treated with diet alone or oral hypoglycemic agents (OHA)³. Therefore, the accurate evaluation of residual pancreatic β -cell function is important for deciding whether insulin treatment is required to control type 2 diabetes. In addition to well-known β -cell function-related parameters, such as HOMA- β , the serum C-peptide itself, the serum C-peptide response to glucagon and the 24-h urinary C-peptide (U-CPR) level^{4–7}, recent reports have shown that the fasting serum

Received 22 May 2013; revised 18 October 2013; accepted 22 October 2013

C-peptide immunoreactivity (CPR) adjusted according to the fasting plasma glucose (FPG) level, such as the CPR index (CPI) and the secretory units of islets in transplantation index (SUIT; developed using the fasting CPR [F-CPR] and the FPG level after islet transplantation), might be useful for evaluating residual pancreatic β -cell function^{8–10}. Furthermore, several reports have examined the correlation between these β -cell function-related parameters and the choice of insulin therapy to achieve glycemic control^{9–16}. However, to the best of our knowledge, no reports have comprehensively compared the abilities of C-peptide-based indices, such as CPI, SUIT and U-CPR, and a serum insulin-based index, such as HOMA- β (which is widely used for assessing the insulin secretory capacity) to predict insulin therapy requirement. Furthermore, as the CPI and SUIT were only recently identified as indices of β -cell function, the relationship between CPI or SUIT and HOMA- β is not fully understood.

With the aforementioned background in mind, we carried out a cross-sectional study to determine the relationship among the β -cell function-related parameters. Then, in a retrospective case–controlled study, we further examined the cut-off values and the utility of β -cell function-related parameters for the prediction of insulin requirement in patients with type 2 diabetes.

MATERIALS AND METHODS

Participants

A total of 442 Japanese patients with type 2 diabetes admitted between October 2006 and April 2011 to the University of Toyama Hospital (Toyama, Japan) for the management of hyperglycemia were selected in the present study. Type 2 diabetes mellitus was diagnosed based on the criteria of the American Diabetes Association (ADA)¹⁷. Among these patients, to compare the abilities of the HOMA- β and the other β -cell function-related parameters to predict insulin requirement, we excluded patients who were already undergoing insulin therapy at the time of admission. In addition, we excluded: (i) patients with a serum creatinine level of 1.5 mg/dL or more; (ii) patients with hepatic dysfunction or malignant disease or who were taking steroids; (iii) patients who could not be clinically followed for at least 12 months; and (iv) patients with a glycosylated hemoglobin A1c (HbA1c) level $>7.0\%$ despite the use of OHA or patients who received insulin, but at a dosage <10 U/day at 12 months after discharge. Finally, 188 inpatients (see Table 1) who received a follow-up examination at least 12 months after discharge were enrolled in the present study.

Measurements

All the measurements were carried out by the Department of Laboratory Medicine, University of Toyama Hospital, Toyama, Japan, using routine automated laboratory methods. The HbA1c level was measured using high-performance liquid chromatography and was expressed as the international

standard value; that is, HbA1c (Japan Diabetes Society [JDS]) + 0.4%, as defined by the JDS^{18,19}. The serum C-peptide level was measured using an electrochemiluminescence immunoassay (C-peptide Kit[®]; Roche Diagnostics, Tokyo, Japan). The serum insulin level was measured using a chemiluminescent enzyme immunoassay (Insulin Kit[®]; Roche Diagnostics).

We measured the FPG, F-CPR, fasting immunoreactive insulin (F-IRI), urinary C-peptide and urinary creatinine levels in the inpatients after overnight fasting on the second or third hospital day, and then calculated the CPI, HOMA- β , HOMA of insulin resistance (IR), and urinary-CPR index (U-CPR index). The CPI and SUIT were calculated as follows^{10,14}: F-CPR (ng/mL) / FPG (mg/dL) $\times 100$, and $1,500 \times$ F-CPR (ng/mL) / (FPG – 61.7), respectively. In addition, the 24-h urinary CPR (U-CPR) was also measured. The U-CPR index was calculated as the U-CPR (μ g/day) / FPG (mg/dL), as previously reported^{10,13}. The HOMA- β and HOMA-IR were calculated as previously reported⁷. Furthermore, we also calculated the HOMA of insulin secretion and HOMA of insulin sensitivity using HOMA2 calculator (<http://www.dtu.ox.ac.uk/homacalculator/>).

Diabetic complications were precisely evaluated during admission. The diagnosis of diabetic retinopathy was carried out by an ophthalmologist.

All the study procedures were approved by the ethics committee of the University of Toyama. Informed consent was obtained from each participant, and anonymity of the participants was preserved during the study.

Treatment Policy and Classification of the Participants

The treatment policy and classification of participants is shown in Figure 1. Lifestyle modification including dietary therapy with an ideal caloric intake calculated from the ideal bodyweight (kg) $\times 25$ – 30 kcal/kg and exercise therapy was introduced during the period of hospital admission. To observe the effect of dietary therapy on the plasma glucose level, in principle, we continued the diabetes therapy that was being received at admission for at least 3 days after admission, except among participants with extremely high plasma glucose levels. In participants who were treated with more than half the maximum dose of sulfonylureas (SU), if the optimal glycemic goal according to the JDS guidelines²⁰ (FPG <130 mg/dL or 2-h postprandial plasma glucose <180 mg/dL) was not achieved within 1 week after admission, intensive insulin therapy was, in principle, started and SU treatment was discontinued. In the remaining participants, if the optimal glycemic goal was not achieved within 1 week after admission, the SU or other OHA dosage was started or increased. Nevertheless, if the optimal glycemic goal was not achieved, intensive insulin therapy was considered. According to our treatment policies for the medications indicated here, to achieve an optimal glycemic goal, we modified the diabetes therapy of the study participants during their admission.

Table 1 | Comparison of clinical characteristics between non-insulin-requiring group and insulin-requiring group

	Total	Non-insulin-requiring group	Insulin-requiring group	<i>P</i> values	<i>P</i> -values* Multivariate
Clinical characteristics at admission					
Age (years)	61.0 ± 12.6	61.6 ± 13.5	60.3 ± 11.1	0.262	
<i>n</i> (Male/female)	188 (126/62)	112 (75/37)	76 (51/25)	0.984	
BMI (kg/m ²)	24.6 ± 4.8	25.3 ± 5.0	23.6 ± 4.4	<0.05	
Waist circumference (cm)	88.6 ± 8.7	90.2 ± 8.4	86.9 ± 8.9	0.052	
Duration of diabetes (years)	8.4 ± 7.8	7.0 ± 7.3	10.5 ± 8.1	<0.01	
Family history of diabetes (%)	51.3	45	60.5	<0.05	
FPG (mg/dL)	176.1 ± 71.1	148.4 ± 51.4	216.5 ± 76.7	<0.001	
HbA1c (%)	9.3 ± 2.3	8.6 ± 2.3	10.3 ± 2.0	<0.001	
eGFR (mL/min)	85.4 ± 26.9	84.2 ± 23.7	87.2 ± 30.3	0.514	
Diabetes therapy before admission					
Untreated	32.4	35.7	27.6	0.245	
Diet alone (%)	11.2	15.2	5.2	<0.05	
Use of oral hypoglycemic agents (%)	56.4	47.3	67.1	<0.01	
Sulfonylureas (%)	43.6	35.7	55.3	<0.01	
Thiazolidinediones (%)	13.8	12.5	15.8	0.521	
Biguanides (%)	16.0	10.7	23.7	<0.01	
α-Glucosidase inhibitor (%)	22.9	12.5	36.8	<0.001	
Glinide (%)	2.7	1.8	3.9	0.366	
DPP-4 inhibitor (%)	1.6	1.8	1.3	0.801	
Complications					
Diabetic retinopathy (%)	30.6	19.6	46.1	<0.001	
Diabetic nephropathy (%)	30	29.9	30.3	0.509	
Diabetic neuropathy (%)	40.9	33.7	51.4	<0.05	
β-Cell function-related indices					
F-CPR (ng/mL)	2.17 ± 0.97	2.28 ± 0.83	2.00 ± 1.14	<0.01	0.255
CPI	1.43 ± 0.88	1.70 ± 0.87	1.03 ± 0.73	<0.001	<0.001
SUIT	45.2 ± 65.7	60.3 ± 80.9	23.9 ± 19.6	<0.001	<0.001
F-IRI	6.65 ± 4.67	7.28 ± 4.73	5.61 ± 4.42	<0.01	0.223
HOMA-IR	2.64 ± 2.03	2.68 ± 2.10	2.70 ± 1.86	0.861	0.842
HOMA-β (%)	34.6 ± 55.8	44.7 ± 67.4	18.2 ± 20.3	<0.001	<0.01
HOMA-S%	158.6 ± 136.2	142.6 ± 116.2	185.1 ± 161.8	0.097	0.073
HOMA-B%	34.8 ± 32.1	43.6 ± 35.3	20.0 ± 18.3	<0.001	<0.001
U-CPR (μg/day)	52.7 ± 42.4	57.6 ± 42.6	45.8 ± 41.4	<0.05	0.723
U-CPR index	0.37 ± 0.35	0.44 ± 0.39	0.27 ± 0.25	<0.001	0.217
Diabetes therapy at discharge					
Diet alone (%)	19.7	32.1	1.3	<0.001	
Sulfonylureas (%)	25.5	32.1	15.8	<0.05	
Thiazolidinediones (%)	6.9	7.1	6.6	0.881	
Biguanides (%)	12.2	14.3	9.2	0.297	
α-Glucosidase inhibitor (%)	21.9	19.6	25.0	0.383	
Glinide (%)	1.6	2.7	0	0.150	
DPP-4 inhibitor (%)	5.3	8.0	1.3	<0.05	
Insulin therapy (%)	47.8	15.2	96.1	<0.001	
Insulin (U/kg/day)	0.32 ± 0.19	0.25 ± 0.05	0.35 ± 0.19	<0.05	
Glycemic control and diabetes therapy at 1 year after discharge					
HbA1c (%)	7.15 ± 1.34	6.66 ± 0.32	7.88 ± 1.50	<0.001	
Diabetes therapy					
Diet alone (%)	18.6	31.3	0	<0.001	
Sulfonylureas (%)	26.1	34.8	13.2	<0.001	
Thiazolidinediones (%)	9.0	11.6	5.3	0.137	
Biguanides (%)	13.8	17.0	9.2	0.131	
α-Glucosidase inhibitor (%)	26.6	24.1	30.2	0.349	

Table 1 (Continued)

	Total	Non-insulin-requiring group	Insulin-requiring group	<i>P</i> values	<i>P</i> -values* Multivariate
Glinide (%)	2.7	2.7	2.6	0.984	
DPP-4 inhibitor (%)	5.3	8.9	0	<0.01	
Insulin (U/kg/day)	–	–	0.32 ± 0.18		

Data are the mean ± standard deviation. Between the non-insulin-requiring group and the insulin-requiring group, the *P*-values were calculated using a Mann–Whitney *U*-test for differences between means, and a χ^2 -test for differences between frequencies. Between the non-insulin-requiring group and the insulin-requiring group, the multivariate *P*-values* were adjusted for age, sex, glycosylated hemoglobin A1c (HbA1c), body mass index (BMI), estimated glomerular filtration rate (eGFR), intake of insulin secretagogue, intake of α -glucosidase inhibitor, intake of biguanides and duration of diabetes. CPI, C-peptide index; DPP-4, dipeptidyl peptidase 4; F-CPR, fasting serum C-peptide immunoreactivity; F-IRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; HOMA- β , homeostasis model assessment of β -cell function; HOMA-B, homeostasis model assessment of insulin secretion using the HOMA2 calculator; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-S, homeostasis model assessment of insulin sensitivity using the HOMA2 calculator; SUIT, secretory units of islets in transplantation index; U-CPR, 24-h urinary C-peptide; U-CPR index, 24-h urinary C-peptide/fasting plasma glucose.

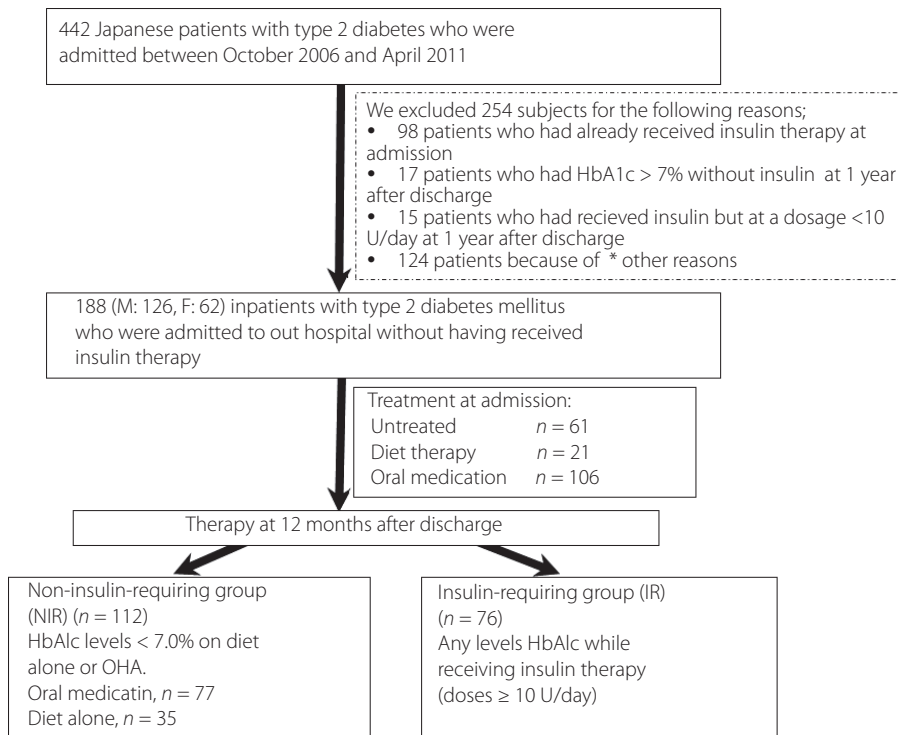


Figure 1 | Classification of study participants. Based on the treatment that was being carried out at 12 months after hospital discharge, we divided the 188 patients into an insulin-requiring group and a non-insulin-requiring group as follows. (a) Insulin-requiring group (IR). Patients who were required to inject more than 10 U of insulin a day continuously were regarded as belonging to the insulin-requiring group. (b) Non-insulin-requiring group (NIR). Patients who were treated with diet alone or oral hypoglycemic agents (OHA), but not with insulin treatment, and had glycosylated hemoglobin A1c (HbA1c) levels < 7.0% at 12 months after discharge were regarded as belonging to the non-insulin-requiring group. *Other reasons: we excluded: (i) patients with a serum creatinine level of 1.5 mg/dL or more; (ii) patients with hepatic dysfunction or malignant disease, or who were taking steroids; and (iii) patients who could not be clinically followed for at least 12 months.

Among the participants who had received intensive insulin therapy, if the optimal glycemic control was maintained at a dosage of <10 U/day of insulin, we discontinued insulin

therapy and started treatment with sulfonylurea and/or another OHA; if the aforementioned criterion was not met, the participants were judged as requiring insulin therapy and

insulin therapy was continued during admission. As a result, 47.8% of the participants were receiving insulin therapy at the time of hospital discharge (Table 1). After hospital discharge, lifestyle modification was also recommended at the time of periodical outpatient visits. Based on the treatment that was being carried out at 12 months after hospital discharge, we divided the 188 patients into an insulin-requiring group and a non-insulin-requiring group as follows:

- Insulin-requiring group (IR): Participants who were required to inject more than 10 U of insulin a day continuously were regarded as belonging to the insulin-requiring group as previously reported^{10,13}.
- Non-insulin-requiring group (NIR): Participants who were treated with diet alone or OHA, but not with insulin treatment, and had HbA1c levels < 7.0% at 12 months after discharge were regarded as belonging to the non-insulin-requiring group.

Statistical Analysis

All the data were expressed as the mean \pm standard deviation. The statistical analyses were carried out using JMP for Windows, Version 8.0 (SAS Institute, Cary, NC, USA). Differences in the clinical features of the NIR and IR subgroups were examined using the Mann–Whitney *U*-test and multiple regression analysis after adjustments for related covariables. The relationships between parameters of β -cell function were investigated using simple and partial regression analysis. A receiver operating characteristic (ROC) curve analysis was carried out to compare the power of several β -cell function-related parameters for predicting the requirement for insulin therapy using the method described previously²¹. We carried out a univariate logistic regression analysis and multivariate logistic analysis to evaluate the effect of several β -cell function and other parameters at admission on the insulin requirement at 1 year after discharge. Results with *P*-values < 0.05 were considered statistically significant.

RESULTS

Correlations Among the β -Cell Function-Related Parameters

The F-CPR, CPI, and SUIT values were all significantly and positively correlated with the HOMA- β (*P* < 0.05; Table 2). However, the correlation coefficient with HOMA- β was the greatest for SUIT (*r* = 0.973, *P* < 0.0001), followed by CPI and then F-CPR (Figure 2, Table 2). The U-CPR and U-CPR index showed a nominal association with each serum parameter of β -cell function (*P* < 0.05), except for the SUIT and HOMA- β (Table 2).

Comparison of the Clinical Characteristics and β -Cell Function-Related Parameters at Admission Between the Insulin-Requiring Group and the Non-Insulin-Requiring Group

Among the 188 participants, 76 participants (40.4%) were receiving insulin treatment at 12 months after discharge

Table 2 | Correlations between C-peptide-based indices and insulin-based indices

	F-CPR	CPI	SUIT	F-IRI	HOMA- β	U-CPR	U-CPR index
Simple correlations coefficients among markers of β -cell function							
F-CPR	–	0.788	0.377	0.825	0.401	0.196	0.192
CPI		–	0.73	0.706	0.733	0.151	0.288
SUIT			–	0.303	0.973	<i>–0.01</i>	<i>0.112</i>
F-IRI				–	0.434	0.281	0.264
HOMA- β					–	<i>0.023</i>	<i>0.125</i>
U-CPR						–	0.879
UCPRI							–
Partial correlations coefficients among markers of β -cell function							
F-CPR	–	0.749	0.265	0.802	0.431	0.196	0.134
CPI		–	0.686	0.665	0.829	0.145	0.224
SUIT			–	0.373	0.974	<i>–0.064</i>	<i>0.025</i>
F-IRI				–	0.485	0.195	<i>0.116</i>
HOMA- β					–	<i>–0.035</i>	<i>0.035</i>
U-CPR						–	0.871
U-CPR index							–

The partial correlation analysis was carried out using independent variables such as age, sex, glycosylated hemoglobin A1c level, body mass index, estimated glomerular filtration rate, intake of insulin secretagogue, intake of α -glucosidase inhibitor, intake of biguanides and duration of diabetes. A value of *P* < 0.05 was obtained for all the comparisons except for the correlation coefficients presented in italics. CPI, C-peptide index; F-CPR, fasting serum C-peptide immunoreactivity; F-IRI, fasting immunoreactive insulin; FPG, fasting plasma glucose; HOMA- β , homeostasis model assessment of β -cell function; SUIT, secretory units of islets in transplantation index; U-CPR, 24-h urinary C-peptide; U-CPR index, 24-h urinary C-peptide/fasting plasma glucose.

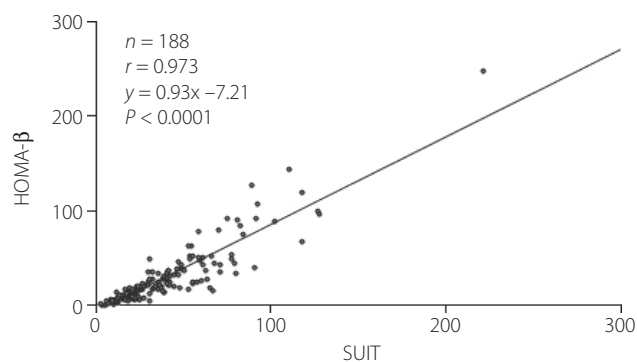


Figure 2 | Correlation between secretory units of islets in transplantation index (SUIT) and homeostasis model assessment of β -cell function (HOMA- β).

(Table 1). Among the patients in the IR group, the mean daily insulin dose was 0.32 ± 0.18 U/kg (19 ± 8 U; range 10–52 U; Table 1). The HbA1c levels in the IR and NIR groups at 12 months after discharge were 7.88% and 6.66% (*P* < 0.001), respectively (Table 1).

Table 3 | Area under the curve of the receiver operating characteristic analysis for the prediction of insulin requirement or non-insulin requirement among β -cell function-related parameters

	Requirement/non-requirement for insulin therapy		Insulin requirement					Non-insulin requirement	
	AUC (95% CI)	<i>P</i> -value compared with SUIT	Cut-off value corresponding to 80% specificity	Sensitivity corresponding to 80% specificity	Cut-off value corresponding to maximal sensitivity plus specificity	Sensitivity (%)	Specificity (%)	Cut-off value corresponding to 80% specificity	Sensitivity corresponding to 80% specificity
F-CPR	0.622 (0.552–0.693)	<0.05	1.50	37.3	1.40	36.0	87.0	2.70	22.2
CPI	0.774 (0.713–0.834)	NS	1.00	61.3	1.14	73.3	71.7	1.42	58.3
SUIT	0.808 (0.751–0.865)	–	23.5	66.7	29.7	78.7	74.1	30.6	71.3
HOMA- β	0.759 (0.694–0.826)	NS	14.9	61.7	14.9	61.7	80.4	24.3	57.7
U-CPR	0.603 (0.529–0.676)	<0.05	22.2	32.9	61.0	80.0	40.0	63.0	40.0
U-CPR index	0.668 (0.596–0.740)	<0.05	0.15	40.0	0.34	77.1	52.1	0.38	47.9

AUC, area under receiver operator characteristics curve; CPI, C-peptide index; F-CPR, fasting serum C-peptide immunoreactivity; HOMA- β , homeostasis model assessment of β -cell function; NS, no significant difference; SUIT, secretory units of islets in transplantation index; U-CPR, 24-h urinary C-peptide; U-CPR index, 24-h urinary C-peptide/fasting plasma glucose.

The clinical characteristics for the two groups at admission are summarized in Table 1. The patients in the IR group had a significantly longer duration of diabetes ($P < 0.01$), a higher percentage of a family history of diabetes mellitus ($P < 0.05$) and a higher HbA1c level ($P < 0.001$) at the time of admission, compared with those in the NIR. The percentage of individuals who had received an oral insulin secretagogue before admission and the incidence of diabetic complications, except for diabetic nephropathy, were also significantly higher in the patients in the IR group than in those in the NIR group ($P < 0.01$ and $P < 0.05$, respectively). The CPI, SUIT and HOMA- β were significantly lower in the patients in the IR group than in those in the NIR group ($P < 0.01$), even after adjustments for confounding factors (Table 1).

Predictive Ability of the β -Cell Function-Related Parameters at Admission

To estimate the abilities of these β -cell function-related parameters to predict insulin requirement, we carried out a ROC analysis. The ROC analysis for insulin requirement showed that the area under the curve (AUC) for SUIT (0.808; 95% CI 0.751–0.865) was significantly larger than those for other parameters of β -cell function, except for the AUC for CPI and that for HOMA- β (Table 3). After SUIT, the CPI and HOMA- β had significantly greater AUC values (AUC for CPI 0.774; 95% CI 0.713–0.834; AUC for HOMA- β 0.759; 95% CI 0.694–0.826) for insulin requirement than the F-CPR itself and U-CPR ($P < 0.05$; Table 3). Setting a cut-off level to obtain a high specificity of at least 80% for insulin requirement, the cut-off values for SUIT, CPI, and HOMA- β were 23.5 (66.7% sensitivity), 1.00 (61.3% sensitivity), and 14.9 (61.7% sensitivity), respectively (Table 3). To examine the effect of FPG or BMI at

admission on the cut-off values and the predictive ability of each index for predicting insulin requirement, we divided the 188 participants into three approximately equally sized strata according to the FPG or BMI at admission (Table 4). The cut-off values for SUIT, CPI and HOMA- β with an over 80% specificity for predicting insulin requirement in the high FPG group were lower than those in the low FPG group. Furthermore, the cut-off values for these indices with an over 80% specificity for predicting insulin requirement in the high BMI group were higher than those in the low BMI group. The AUC values of the ROC analysis for predicting insulin requirement were not significantly different among SUIT, CPI and HOMA- β in each stratum. The AUC of the ROC analysis for predicting insulin requirement of CPI and SUIT tended to be lower in the high FPG group than in the low FPG group, whereas those of all three indices were comparable in the three groups divided according to the BMI at admission.

Association of the β -Cell Function-Related Parameters and Other Clinical Parameters at Admission with Insulin Requirement

Finally, to evaluate the effect of several β -cell function and other parameters at admission on the insulin requirement, we carried out univariate logistic regression analyses (Table 5). Then, we incorporated the variables that were significantly related to IR as explanatory variables in a multivariate logistic analysis (Table 6). As a result, pretreatment with sulfonylurea and the HbA1c level at admission were identified as independent predictors of insulin requirement in all the models in addition to CPI, SUIT, and HOMA- β (Table 6). In addition, the ROC analysis for insulin requirement also showed that the AUC for HbA1c level at admission (0.723; 95% CI

Table 4 | Effect of fasting plasma glucose and body mass index at admission on the cut-off values, and the ability of the C-peptide index, secretory units of islets in transplantation index, and homeostasis model assessment of β -cell function to predict insulin requirement according to receiver operating characteristic analysis

Classification of three groups according to FPG at admission				
FPG (mg/dL)	All patients	66–134	135–190	191–549
<i>n</i> (Male/female)	188 (126/62)	62 (39/23)	62 (37/25)	63 (50/13)
Age (years)	61.0 \pm 12.6	62.6 \pm 12.2	61.1 \pm 12.1	59.4 \pm 13.4
FPG	176.1 \pm 71.1	113 \pm 14.5	160 \pm 16.8	254.1 \pm 65.4
BMI	24.6 \pm 4.8	25.6 \pm 5.7	24.6 \pm 4.7	23.7 \pm 3.8
Insulin requirement (%)	40.6	9.7	43.6	68.3
Cut-off value for over 80% specificity for the prediction of insulin requirement				
CPI	1.00	1.29	1.08	0.69
SUIT	23.5	41.7	25.3	12.9
HOMA- β	14.9	23.1	14.9	7.4
AUC of the ROC analysis for the prediction of insulin requirement				
CPI	0.774	0.687	0.661	0.575
SUIT	0.808	0.704	0.684	0.601
HOMA- β	0.759	0.548	0.675	0.628

Classification of three groups according to BMI at admission				
BMI (kg/m ²)	All subjects	14–22.8	23–25.9	26–57.2
No. (M/F)	188 (126/62)	63 (45/18)	66 (45/21)	59 (36/23)
Age (years)	61.0 \pm 12.6	63.0 \pm 9.7	64.3 \pm 12.1	55.4 \pm 14.1
FPG	176.1 \pm 71.1	186.6 \pm 82.4	173.3 \pm 57.1	167.9 \pm 72.2
BMI	24.6 \pm 4.8	20.3 \pm 1.9	24.5 \pm 0.9	29.4 \pm 5.1
Insulin requirement (%)	40.6	54.0	37.9	28.8
Cut-off value for over 80% specificity for insulin requirement				
CPI	1.00	0.79	1.02	1.11
SUIT	23.5	19.3	29.7	28.6
HOMA- β	14.9	8.7	13.8	21.2
AUC of the ROC analysis for the prediction of insulin requirement				
CPI	0.774	0.736	0.732	0.764
SUIT	0.808	0.773	0.793	0.788
HOMA- β	0.759	0.759	0.734	0.768

Data are the mean \pm standard deviation. AUC, area under receiver-operator characteristics curve; BMI, body mass index; CPI, C-peptide index; FPG, fasting plasma glucose; HOMA- β , homeostasis model assessment of β -cell function; ROC, receiver operating characteristic; SUIT, secretory units of islets in transplantation index.

0.659–0.787) was comparable with that for HOMA- β (Table S1).

DISCUSSION

In the present study, it was found that: (i) the correlation with HOMA- β was the greatest for SUIT, followed by CPI and the least for F-CPR; (ii) patients who required insulin therapy had a lower SUIT, CPI and HOMA- β at the time of admission, even after adjustments for confounding factors; (iii) among the β -cell function-related parameters, SUIT had the greatest AUC in the ROC analysis for predicting insulin requirement, followed by CPI and HOMA- β ; and (iv) the cut-off values for SUIT, CPI, and HOMA- β with an over 80% specificity for the prediction of insulin requirement were affected by FPG and BMI at admission.

One of the most important points in the present study was the strict selection of patients who belonged to the non-insulin-requiring group (NIR). To validate the patients who did not require insulin therapy, we selected patients who achieved a glycemic control of HbA1c < 7.0% with diet alone or OHA, but not with insulin treatment, at 1 year after discharge; these patients were considered to belong to the NIR group. Without these criteria, patients who failed to achieve good blood glucose control without insulin therapy, either partly because of their rejection of insulin therapy or because of mistakes in their treatment made by diabetologists, would have been included in the NIR group; as a result, the cut-off level and the predictive ability of β -cell-related parameters for insulin requirement might not have been accurately determined. Several reports examining the correlation between the levels of

Table 5 | Univariate logistic regression analysis for the prediction of insulin requirement

Variables	Odds ratio (95% CI)	P-value
Age (years)	0.99 (0.97–1.02)	0.488
Sex (male = 1, Female = 0)	1.01 (0.54–1.88)	0.983
Duration of diabetes (years)	1.06 (1.02–1.11)	<0.01
Family history of diabetes (yes = 1, no = 0)	1.88 (1.04–3.43)	<0.05
BMI	0.91 (0.84–0.98)	<0.05
HbA1c at admission	1.41 (1.22–1.64)	<0.001
eGFR	1.00 (0.99–1.02)	0.451
Intake of sulfonylurea at admission (yes = 1, no = 0)	2.22 (1.23–4.06)	<0.01
Intake of α -glucosidase inhibitor at admission (yes = 1, no = 0)	1.83 (1.15–3.85)	<0.01
Intake of biguanides at admission (yes = 1, no = 0)	1.63 (1.05–3.57)	<0.05
Diabetic retinopathy (yes = 1, no = 0)	3.50 (1.83–6.83)	<0.001
Diabetic nephropathy (yes = 1, no = 0)	1.02 (0.53–1.93)	0.959
Diabetic neuropathy (yes = 1, no = 0)	2.09 (1.12–3.92)	<0.05
F-CPR (ng/mL)	0.72 (0.52–0.99)	<0.05
CPI	0.25 (0.14–0.42)	<0.001
SUIT	0.95 (0.93–0.97)	<0.001
HOMA-IR	1.00 (0.85–1.18)	0.953
HOMA- β (%)	0.96 (0.94–0.98)	<0.001
U-CPR (μ g/day)	0.99 (0.98–1.00)	0.069
U-CPR index	0.12 (0.03–0.40)	<0.001

CI, confidence interval; CPI, C-peptide index; eGFR, estimated glomerular filtration rate; F-CPR, fasting serum C-peptide immunoreactivity; HOMA- β , homeostasis model assessment of β -cell function; HOMA-IR, homeostasis model assessment of insulin resistance; SUIT, secretory units of islets in transplantation index; U-CPR, 24-h urinary C-peptide; U-CPR index, 24-h urinary C-peptide/fasting plasma glucose.

endogenous insulin secretion and the insulin requirement have been carried out in Japanese diabetic patients^{10,13,14,16}. However, in these reports, the glycemic goal was not described clearly¹⁰, and patients with insufficient glycemic control with OHA were sometimes included in the NIR group^{13,16}, except in one recent study¹⁴. Furthermore, in that study¹⁴, they observed the relationship between glycemic control and diabetes treatment in participants only during the period of hospitalization. We believe that this observation period is too short to judge whether insulin therapy is required, as most patients are unable to maintain good glycemic control after discharge because of inappropriate lifestyle behaviors. Therefore, the present study is the first report to examine the predictive ability and the cut-off level of β -cell function-related parameters for insulin requirement using strict inclusion criteria for the NIR group and with a sufficient observation period.

Regarding the selection of the participants belonging to the insulin-requiring group (IR), we selected these participants for the following reasons. In the study examining the clinical parameters for predicting the possibility of insulin therapy withdrawal carried out in Japanese patients with type 2 diabetes mellitus, it has been reported that the patients, who had been treated with an insulin dose <14 U/day, were able to be withdrawn from insulin therapy after receiving intensive therapy²². In addition, we quoted the criterion of the IR group as previously reported^{10,13}; as a result, we defined the participants who were required to inject more than 10 U of insulin a day continuously as the IR group.

Also importantly, the present study is the first to compare not only C-peptide-based indices (either serum or urinary), but also HOMA- β , which is widely used for assessing the insulin secretory capacity³. Previous reports compared only C-peptide-based indices^{9–11,13–16}. Although Taverna *et al.*¹² reported that HOMA- β was a good predictor of the insulin-requiring stage in type 2 diabetes, they did not compare the abilities of HOMA- β and other β -cell function-related indices to predict insulin requirement¹². Here, we showed for the first time that among the C-peptide-based indices and HOMA- β , SUIT had the best ability to predict insulin requirement, and that the CPI was comparable with HOMA- β in its predictive ability.

SUIT was developed using F-CPR and the FPG level after islet transplantation, and reported to be correlated with the glucagon stimulated C-peptide levels not only in islet-transplanted patients, but also in type 2 patients⁸. This index was originally developed on the assumption that when the FPG falls to 61.7 mg/dL, endogenous insulin secretion reaches zero. In contrast, in the case of the CPI, when the FPG reaches zero, the serum C-peptide is assumed to be zero, which does not reflect the physiological situation. Therefore, we speculated that as the formula for SUIT reflected the physiological endogenous insulin secretion more closely than the formula for CPI, SUIT might be a better predictor of the insulin requirement, compared with CPI, in the present study. SUIT resembles HOMA- β in that its formula assumes that insulin secretion is suppressed to zero at approximately 60 mg/dL of glucose; in the present study, we showed that SUIT was more strongly correlated with HOMA- β ($r = 0.973$, $P < 0.0001$; Figure 2, Table 2) than with other β -cell function-related parameters. However, HOMA- β had a lower ability to predict insulin requirement than SUIT. We speculated that this finding might have reflected metabolic differences between serum C-peptide and insulin; specifically, C-peptide is split from insulin in the secretory granules of β -cells and is co-secreted with insulin; then insulin, but not C-peptide, is extracted by the liver²³.

We also examined the effect of FPG or BMI at admission on the cut-off value for the prediction of insulin requirement. The cut-off values of SUIT, CPI, and HOMA- β for an over 80% specificity for the prediction of insulin requirement were lower

Table 6 | Multivariate logistic regression analysis for the prediction of insulin requirement

Variables	Model 1		Model 2		Model 3	
	Adjusted odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
Duration of diabetes (years)	1.02 (0.96–1.09)	0.473	1.03 (0.97–1.10)	0.343	1.02 (0.95–1.09)	0.582
Family history of diabetes (yes = 1, no = 0)	1.63 (0.76–3.55)	0.211	2.62 (1.16–6.11)	<0.05	1.80 (0.82–3.99)	0.143
BMI	0.99 (0.89–1.09)	0.800	1.00 (0.89–1.11)	0.943	0.99 (0.90–1.09)	0.873
HbA1c at admission	1.28 (1.05–1.59)	<0.05	1.30 (1.05–1.65)	<0.05	1.23 (1.01–1.48)	<0.05
Intake of sulfonylurea at admission (yes = 1, no = 0)	3.77 (1.63–9.35)	<0.01	3.25 (1.37–8.13)	<0.01	3.77 (1.60–9.46)	<0.01
Intake of α -GI at admission (yes = 1, no = 0)	2.09 (0.79–5.74)	0.139	2.00 (0.69–6.01)	0.202	2.14 (0.79–6.01)	0.134
Intake of biguanides at admission (yes = 1, no = 0)	1.69 (0.48–6.17)	0.409	1.38 (0.32–6.00)	0.662	1.73 (0.45–7.10)	0.426
Diabetic retinopathy (yes = 1, no = 0)	2.69 (1.06–7.09)	<0.05	2.26 (0.87–6.00)	0.095	2.98 (1.12–8.31)	<0.05
Diabetic neuropathy (yes = 1, no = 0)	1.97 (0.86–4.57)	0.108	1.83 (0.76–4.43)	0.175	1.80 (0.82–3.99)	0.099
CPI	0.26 (0.12–0.53)	<0.001	–	–	–	–
HOMA- β	–	–	0.97 (0.94–0.99)	<0.01	–	–
SUIT	–	–	–	–	0.95 (0.92–0.97)	<0.001

Multivariate logistic regression analyses were carried out in models 1–3. Model 1 was adjusted for duration of diabetes, family history of diabetes, body mass index (BMI), glycosylated hemoglobin A1c (HbA1c) at admission, intake of insulin secretagogue, intake of α -glucosidase inhibitor (α -GI), intake of biguanides, presence of diabetic complications (diabetic retinopathy and diabetic neuropathy) and C-peptide index (CPI). Model 2 was adjusted for all the variables included in model 1 except for CPI and with the addition of homeostasis model assessment of β -cell function (HOMA- β). Model 3 was adjusted for all the variables included in model 1 except for CPI and with the addition of secretory units of islets in transplantation index (SUIT). CI, confidence interval.

in the high FPG group and higher in the high BMI group. A higher FPG at admission might have impaired endogenous insulin secretion because of the glucose toxicity effect, resulting in lower values for each parameter. It is also possible that as a higher BMI is associated with insulin resistance, the cut-off values for the prediction of insulin requirement were higher to compensate for the increased demand of insulin to control blood glucose levels. These findings show that the cut-off value for the prediction of insulin requirement was affected by the FPG and BMI at admission.

The present study had several limitations. First, this study was a retrospective analysis of inpatients at one hospital. Second, we also included patients whose FPG was 200 mg/dL or more, although the HOMA- β was reported to be valid within 234 mg/dL of FPG⁷. We also excluded 34 patients whose FPG was 234 mg/dL or more and re-analyzed the predictive ability of the β -cell function-related parameters in 154 patients with type 2 diabetes. However, we obtained results that were similar (CPI, AUC = 0.729; SUIT, AUC = 0.771; HOMA- β , AUC = 0.693) to those obtained in participants including whose FPG was 234 mg/dL or more. Third, we did not measure the plasma glucagon-stimulated C-peptide level or the postprandial C-peptide to glucose ratio (PGCR). The former is well known as a gold standard test to evaluate β -cell function²⁴, whereas the latter was recently reported to be a better predictor of insulin requirement than the fasting CPI^{10,25}. Unfortunately, as we did not measure these parameters, we were unable to compare the usefulness of these indices with those of fasting CPI, SUIT and HOMA- β . Fourth, among the 442 patients with type 2 diabetes who were admitted to our hospital during a

period of approximately 5 years, to compare the ability of HOMA- β and the C peptide-related index to predict insulin requirement, and to recruit patients according to the strict inclusion criteria for insulin requirement, we excluded many patients from the present study (Figure 1). The patients who were excluded from this study had a longer duration of diabetes, and a lower insulin secretion than those who were included in this study (Table S2). Therefore, these selection biases might have slightly affected our conclusion. Fifth, we did not fully examine the changes in treatment during the follow-up period after discharge. In the present study, during the 1-year period after hospital discharge, 15.2% of the participants in the NIR group stopped receiving insulin therapy, and 3.9% of the participants in the IR group started receiving insulin therapy. Therefore, these changes in diabetes treatment after hospital discharge might have slightly affected the conclusion of this study. Sixth, incretin therapy, such as the use of dipeptidyl peptidase 4 (DPP-4) inhibitor, has recently been frequently used in the treatment of type 2 diabetes. However, in the present study, only a small proportion (1.3%) of the participants were treated with DPP-4 inhibitor. The addition of DPP-4 inhibitor has been reported to decrease the HbA1c level effectively in patients with insufficient glycemic control despite the use of SU, probably because DPP-4 inhibitor and SU are thought to stimulate insulin secretion in a coordinated and synergistic manner^{26,27}. Therefore, if the patients treated with DPP-4 inhibitor became a larger proportion of the study participants, the cut off value of β -cell function-related parameters for insulin requirement might change. Seventh, the number of events per variable was <10 in the multivariate logistic

regression analysis (Table 6), so the results should be interpreted with caution²⁸.

In conclusion, among the indices of β -cell function examined in the present study, SUIT was the best predictive marker of insulin requirement. However, this study was carried out retrospectively. A prospective study involving a larger number of participants is required to clarify the present findings.

ACKNOWLEDGMENT

None of the authors have any conflicts of interest.

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SUPPORTING INFORMATION

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

Table S1 | Area under the curve of the receiver operating characteristic analysis for the prediction of insulin requirement of fasting plasma glucose, glycosylated hemoglobin A1c, body mass index and homeostasis model assessment of insulin resistance at admission.

Table S2 | Comparison of clinical characteristics between patients who were included in this study and those who were excluded.