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Correlation of Serum CPR to Plasma Glucose Ratio with Various Indices of Insulin Secretion and Diseases Duration in Type 2 Diabetes

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Evaluating insulin secretion ability and sensitivity is essential to establish an appropriate treatment for patients with type 2 diabetes. The serum C-peptide response (CPR) level is used to evaluate the quantity of endogenous insulin secretion. However, the serum CPR level alone cannot indicate insulin-secretion ability or insulin sensitivity, because plasma glucose levels influence endogenous insulin secretion and vice versa.

The CPR index, a ratio of serum CPR level to plasma glucose concentration when measured simultaneously, was previously reported to be a useful marker to determine the necessity of insulin treatment in patients with type 2 diabetes, but the reasons are unknown. The aim of this study was to clarify which factors affect the CPR index in patients with type 2 diabetes. Totally, 121 subjects were included in this study; all participants were hospitalized for type 2 diabetes. On the day after admission, we calculated the CPR index from each patient's fasting blood sample and a blood sample taken 2 hours after breakfast (the postprandial sample). A detailed medical history was taken from each patient to establish the disease duration. The degree of diabetic retinopathy judged by an ophthalmologist was obtained from patients' medical records. An oral glucose tolerance test and a glucagon load test were performed after the fasting plasma glucose level decreased to 130 mg/dl, and indices of insulin secretion and sensitivity were calculated.

Fasting and postprandial CPR indices were moderately correlated with total endogenous insulin secretion after oral glucose load and with the CPR level after glucagon load, insulin sensitivity, composite index, and the reciprocal index of homeostasis model assessment (HOMA-R^{-1}). Furthermore, there was a weak but significant correlation between the postprandial CPR index and the duration of diabetes. The postprandial CPR index was inversely correlated with the degree of diabetic retinopathy, which is known to be associated with the duration of hyperglycemia. Our data clearly shows that the CPR index is a useful parameter to reflect the degree of impaired glucose tolerance.

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INTRODUCION

In the pathogenesis of type 2 diabetes, the insulin secretion capacity of pancreatic β-cells and the insulin sensitivity of target organs are both affected to some degree [1-2]. Therefore, it is necessary to evaluate the insulin-secretion capacity and insulin sensitivity in each patient to establish the appropriate type 2 diabetes treatment [2]. The serum C-peptide response (CPR) level is used to quantify endogenous insulin secretion. However, the serum CPR level alone cannot indicate insulin-secretion ability or insulin sensitivity because the plasma glucose level and the amount of endogenous insulin secretion influence each other. On the other hand, the CPR index (CPI) has previously been reported as a useful marker to establish the necessity of insulin treatment in patients with type 2 diabetes [3-7], but the reason is unknown. The CPI is a ratio of the serum CPR level to the plasma glucose concentration measured simultaneously (calculated as serum CPR level (ng/ml)/plasma glucose concentration (mg/ dl) × 100). The aim of this study was to clarify the utility of the CPR index in patients with type 2 diabetes.

SUBJECTS AND METHODS

Subjects

The study subjects were patients with type 2 diabetes who were admitted to Kobe University Hospital for glycemic control from March 2008 to January 2011. Participants were aged 19–82 years and did not have severe renal dysfunction (CCR ≤ 60 mL/[min·1.73 m^2]), liver dysfunction (aspirate aminotransferase or alanine aminotransferase level ≥ 50 IU/mL), or insulin antibody levels of ≥20%. Participants were not insulin users and did not previously undergo laser treatment for advanced diabetic retinopathy. A total of 121 patients were enrolled in the study. Shown in Table I are the basal characteristics of the study subjects. The values of glycated hemoglobin (HbA1c) were expressed as National Glycohemoglobin Standardization Program (NGSP) values calculated from Japan Diabetes Society (JDS) values. On admission, the numbers of patients on different anti-diabetic

Table I. Basal characteristics of the study participants

Numbers	121
Gender (male/female)	71/50
Age (years)	58.7 ± 13.4
BMI (kg/m^2)	26.2 ± 5.8
Duration (years)	8.9 ± 8.3
FPG (mg/dl)	137.8 ± 47.9
F-IRI (μU/ml)	10.3 ± 26.6
F-CPR (ng/ml)	2.22 ± 1.73
F-CPI	1.64 ± 0.81
PPPG (mg/dl)	234.2 ± 86.0
PP-CPR (ng/ml))	6.23 ± 2.88
PP-CPI	3.15 ± 2.07
HbA1c	8.2 ± 1.7

Data are shown as mean ± SD. BMI, body mass index; FPG, fasting plasma glucose; F-IRI, fasting plasma immunoreactive insulin concentration; F-CPR, fasting serum C-peptide response; F-CPI, fasting CPR index; PPPG, postprandial plasma glucose; pp-CPI, postprandial CPR index

medications were as follows: sulphonylurea, 68; glinide, 4; pioglitazone, 20; metformin, 53; α-glucosidase inhibitor, 27; and dipeptidyl peptidase-4 inhibitor, 7. This study was approved by the Ethics Committee of Kobe University Graduate School of Medicine and registered with the university Hospital Medical Information network (UMIN 000002359). Written informed consent was obtained from all study participants.

Methods

On the morning after admission, fasting blood samples were taken from all participants, followed by blood samples taken 2 h after consuming a standard breakfast. The total calorie content of a participant's standard meal was 28 kcal/ideal body weight/day, and the meal comprised 60% carbohydrate, 20% fat, and 20% protein. The ratio of the serum CPR level (ng/mL) to the plasma glucose concentration (mg/dL) multiplied by 100 at each sampling point was calculated to determine the CPR indices. The fasting-CPR index (F-CPI) was calculated from fasting blood samples, and the postprandial-CPR index (PP-CPI) was calculated from blood samples taken 2 h after breakfast. When target glucose levels were achieved (fasting plasma glucose level < 130 mg/dL), the 75-g oral glucose-tolerance test (OGTT) and a glucagon challenge test were performed. In the glucagon challenge test, 1 mg of glucagon was administered intravenously within 30 s, and the serum level of CPR was measured 6 min after the challenge (CPR_6). The insulinogenic index (II), ΣCPR, composite index, and reciprocal of homeostasis model assessment of insulin resistance (HOMA-R^{-1}) were calculated as follows:

$II = (IRI_{30} - IRI_0)/(PG_{30} - PG_0)$ (8)

$\Sigma CPR = CPR_0 + CPR_{30} + CPR_{60} + CPR_{90} + CPR_{120}$ (9)

Composite index = $10000/SQRT\ [(PG_0 \times IRI_0) \times (\text{mean PG} \times \text{mean IRI})]$ (10)

HOMA-$R^{-1} = (PG_0 \times IRI_0/405)^{-1}$ (11)

PGx: plasma glucose concentration at x min after glucose load

IRIx: immunoreactive insulin level at x min after glucose load

CPRx: CPR level at x min after glucose load

A detailed medical history was taken from all participants to establish the disease duration. The degree of diabetic retinopathy was judged by an ophthalmologist by analysis of patients' medical records.

Statistical analysis

Statistical analysis was carried out with the Stat View 5.0 system (SAS Institute, Carry, NC). Clinical data were presented as mean ± standard deviation. Simple liner regression analysis was used for assessing correlation. We used the Kruskal–Wallis test to compare variables across groups. Post-hoc comparisons were made with the Tukey–Kramer method. A P-value of <0.05 was considered statistically significant.

RESULTS

Correlation analyses of insulin secretion parameters showed that F-CPI and PP-CPI were weakly correlated with the insulinogenic index, which is considered an early insulin secretion index ($r = 0.359$, $p < 0.0001$ for F-CPI; $r = 0.457$, $p < 0.0001$ for PP-CPI; Fig. 1a, b). However, F-CPI and PP-CPI were strongly correlated with ΣCPR, which is representative of the total insulin secretion during an OGTT ($r = 0.582$, $p < 0.0001$ for F-CPI; $r = 0\ .635$, $p < 0.0001$ for PP-CPI; Fig. 1c, d). F-CPI was also strongly correlated with CPR_6, which is a measure of insulin secretion capacity ($r = 0.562$, $p < 0.0001$; Fig. 1e, f).

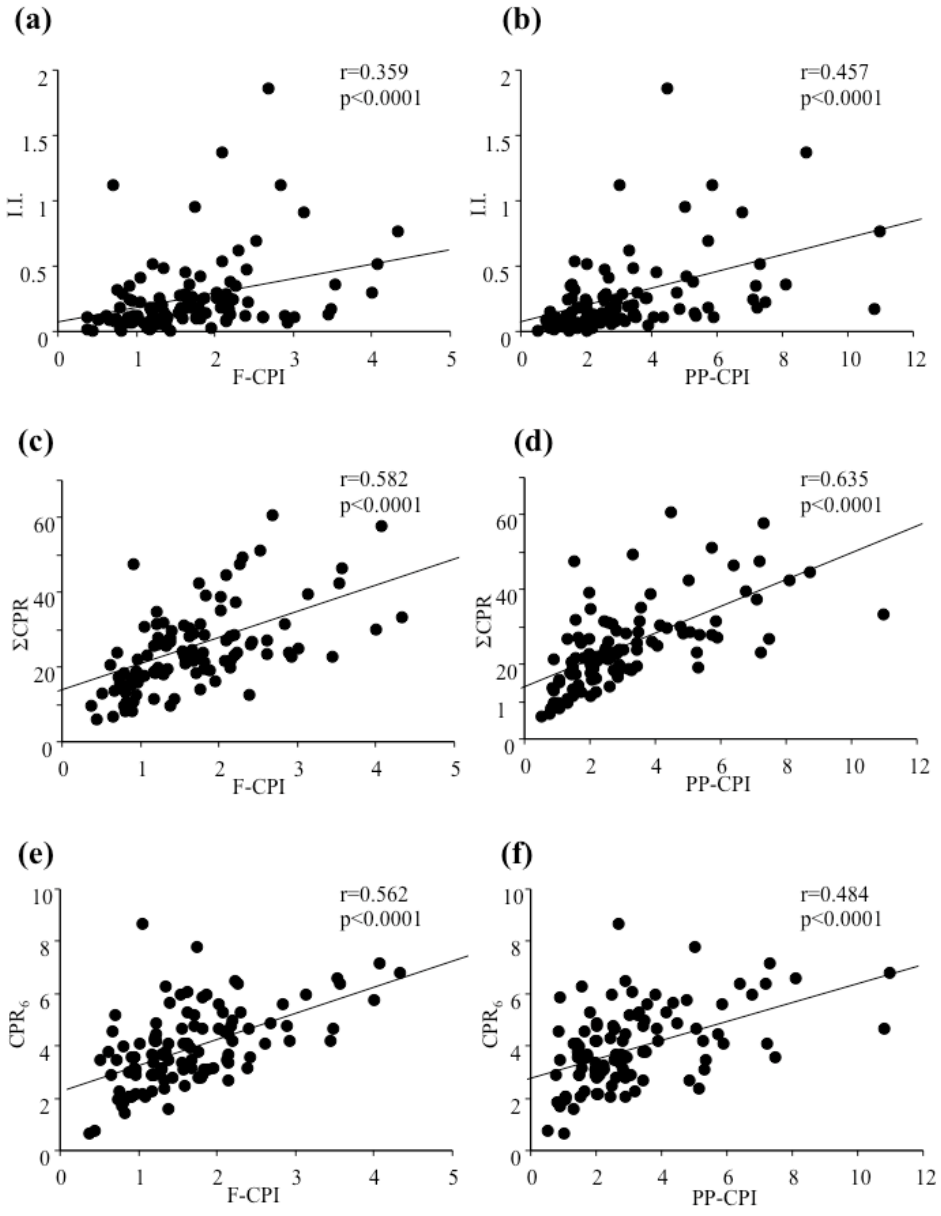

Fig. 1. Correlation of the CPR index and insulin secretion parameters. Graphs represent a correlation between (a) fasting CPR index and II; (b) postprandial CPR index and II; (c) fasting CPR index and ΣCPR; (d) postprandial CPR index and ΣCPR; (e) fasting CPR index and CPR_6; (f) postprandial CPR index and CPR_6. Pearson's correlation coefficient (r) is shown. F-CPI, fasting CPR index; PP-CPI, postprandial CPR index; II, insulinogenic index; ΣCPR, sum of serum CPR level at each time point during oral glucose tolerance test; CPR_6, serum C-peptide response level 6 min after glucagon load.

In the analysis of insulin sensitivity parameters, F-CPI was weakly but significantly correlated with HOMA-R^{-1}, an insulin sensitivity parameter in the resting state ($r = –0.373$, $p < 0.0001$; Fig. 2a). Additionally, F-CPI and PP-CPI were weakly but significantly correlated with the composite index ($r = –0.452$, $p < 0.0001$ for F-CPR; $r = –0.354$, $p = 0.0003$ for PP-CPI; Fig. 2c, d), which is indicative of whole-body insulin sensitivity.

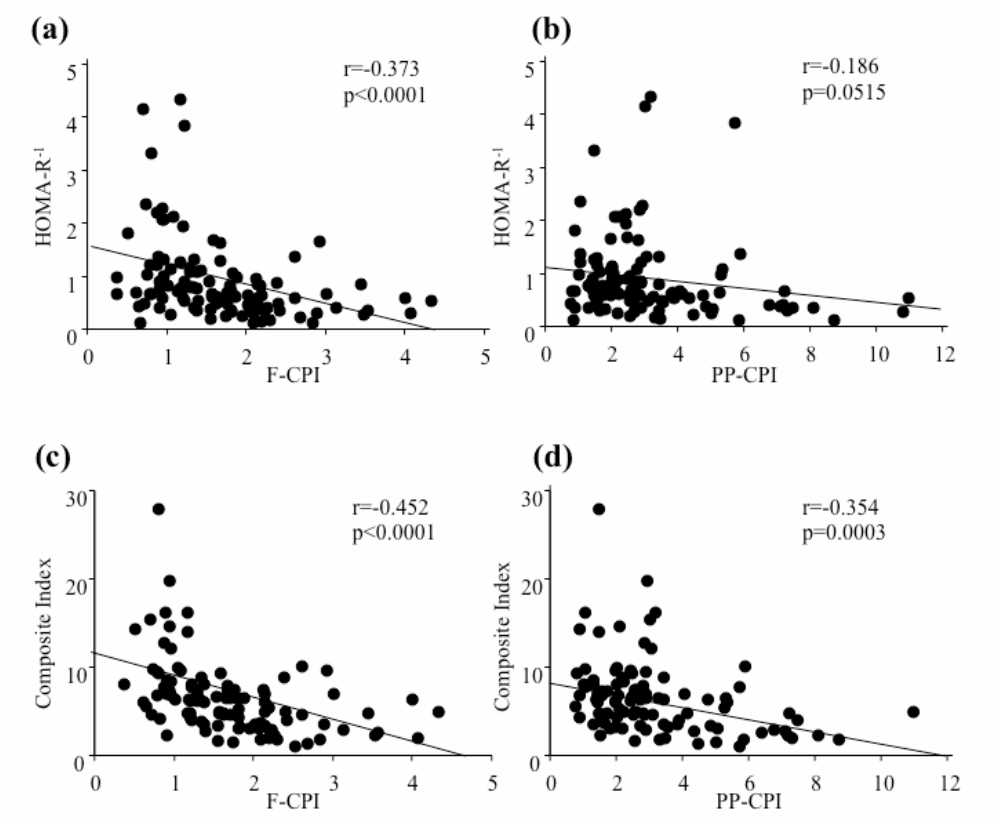

Fig. 2. Correlation of CPR index and insulin sensitivity parameters. Graphs represent correlation between (a) fasting CPR index and HOMA-R^{-1}; (b) postprandial CPR index and HOMA-R^{-1}; (c) fasting CPR index and composite index; (d) postprandial CPR index and composite index. Pearson's correlation coefficient (r) is shown. F-CPI, fasting CPR index; PP-CPI, postprandial CPR index; HOMA-R^{-1}, reciprocal of homeostasis model assessment of insulin resistance; composite index, composite insulin sensitivity index.

The results of the correlation analyses shown in Figures 1–2 are summarized in Table II.

Table II. Correlation of F-CPI and PP-CPI with various indices for insulin secretion and insulin sensitivity

	F-CPI		PP-CPI	
	r	p	r	P
Insulinogenic index	0.359	<0.0001	0.457	<0.0001
ΣCPR (ng/mL)	0.582	<0.0001	0.635	<0.0001
CPR_6 (ng/mL)	0.562	<0.0001	0.484	<0.0001
HOMA-R^{-1}	-0.373	<0.0001	-0.186	0.0515
Composite index	-0.452	<0.0001	-0.354	0.0003

Pearson's correlation coefficient (r) is shown. ΣCPR, sum of serum C-peptide response level at each time points during the oral glucose-tolerance test. ; CPR_6, serum C-peptide response level 6 min after glucagon load; HOMA-R^{-1}, reciprocal of homeostasis model assessment of insulin resistance; composite index, composite insulin sensitivity index.

When analyzing the correlation between diabetes duration and the CPR indices, disease duration was split into 3 groups: less than 10 years (n = 81), from 10 to 20 years (n = 29), and more than 20 years (n = 11). F-CPI was not correlated with disease duration (r = –0.236, p = 0.0085; Fig. 3a, b), but PP-CPI was found to be correlated with disease duration across the 3 groups (r = –0.339, p < 0.0001; Fig. 3c, d).

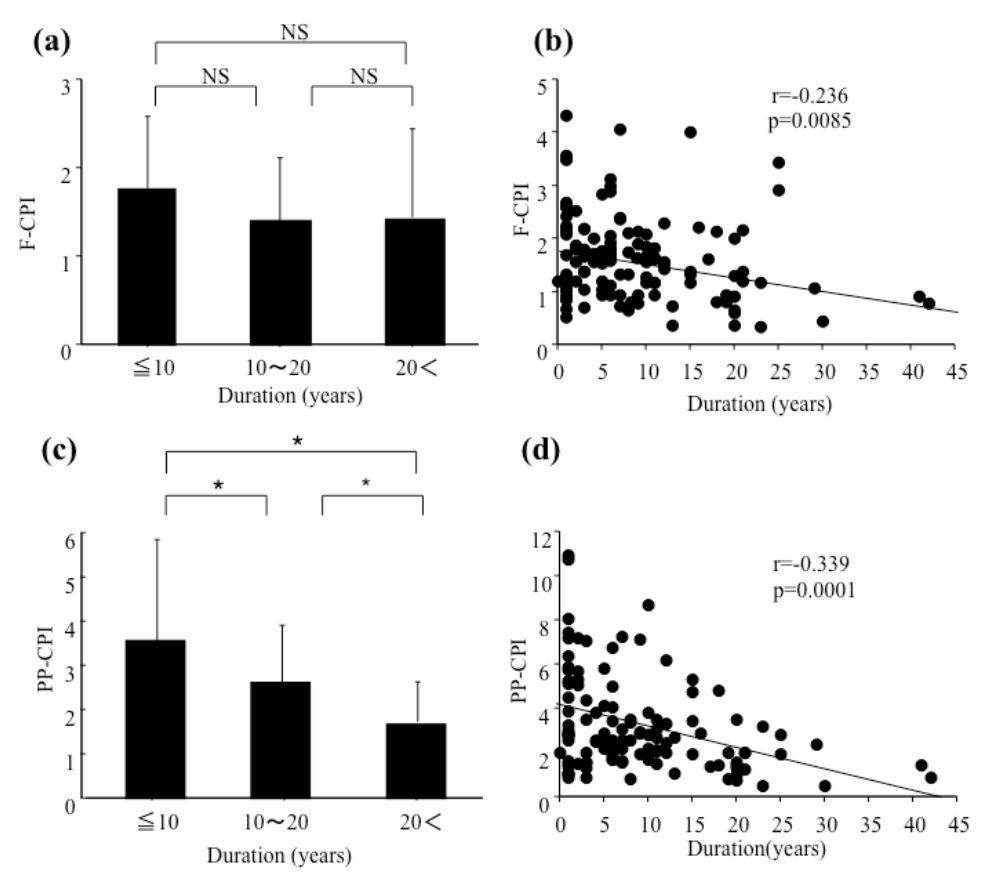

Fig. 3. Correlation between CPR indices and disease duration. Correlation was found with PP-CPI, but not F-CPI. (a) Difference in F-CPI between different disease duration groups. Data are shown as mean ± SD. (b) Correlation of F-CPI with disease duration. Pearson's correlation coefficient (r) is shown. (c) Difference in PP-CPI between disease duration groups (*P < 0.05; Kruskal-Wallis analysis). (d) Correlation of PP-CPI with disease duration. F-CPI, fasting CPR index; PP-CPI, postprandial CPR index; NS, not significant

To assess the relationship between CPR indices and the degree of diabetic retinopathy (DR), patients were divided into 3 groups: no DR (n = 99), simple DR (n = 13), and

pre-proliferative DR (PrePDR) with proliferative DR (PDR) (PrePDR, n = 5; PDR, n = 4; total, n = 9). PP-CPI was found to decrease as DR progressed (Fig. 4).

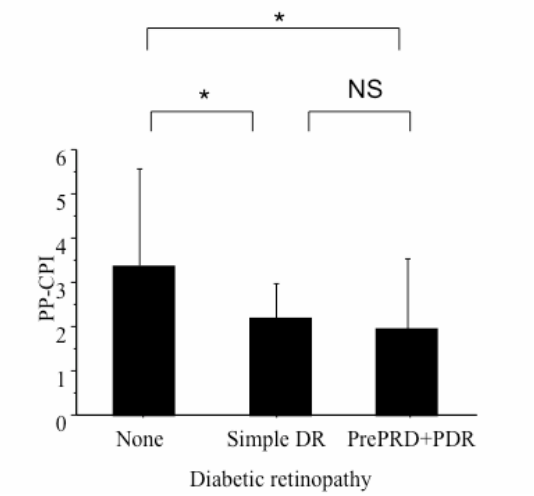

Fig. 4. Differences in PP-CPI between the groups divided by degree of diabetic retinopathy. None, no diabetic retinopathy; simple DR, simple diabetic retinopathy; PrePDR + PPDR, preproliferative diabetic retinopathy with proliferative diabetic retinopathy. Data are shown as the mean ± SD. *P < 0.05 (Tukey–Kramer analysis)

DISCUSSION

There have been previous reports on the clinical utility of the CPR index, which is calculated by the ratio of the serum CPR value against the plasma glucose level, in patients with type 2 diabetes. Peacock et al. reported in 1984 that the fasting serum CPR level categorized according to the plasma glucose concentration, i.e., the fasting CPR index, would be a better index than the fasting serum CPR level alone to determine whether blood glucose control would be improved by introducing insulin [3]. However, in the 1980s, insulin products and sulfonylurea doses used in clinical practice were different from those used today; therefore, it is necessary to re-evaluate the utility of the CPR index.

In recent years, several studies have shown that the F-CPI is a useful marker to indicate whether a patient will benefit from insulin treatment [3-7]. Asano et al. reported that the specificity of F-CPI is approximately 90%, assuming that a patient with an F-CPI value of 0.8 or less would need insulin treatment and a patient with an F-CPI value of 1.8 or more would not need insulin treatment [4]. Actually, we previously conducted a similar analysis in 132 patients with type 2 diabetes, and our results were in accordance with those of previous reports; we found sensitivity and specificity values of 69% and 79% for F-CPI, respectively, assuming that a patient should be given insulin treatment if the F-CPI value is 1.17 or less (unpublished observation). Furthermore, Saisho et al. examined the usefulness of PP-CPI using receiver-operating characteristic curve analysis and reported that PP-CPI was a more useful index to determine the necessity of insulin treatment than F-CPI [7]. Additionally we also got similar results in 132 patients with type 2 diabetes, that the sensitivity and the specificity values was 78% and 82% for PP-CPI, respectively, assuming that a patient should be given insulin treatment if the PP-CPI value is 1.94 or less, and we confirmed that found

PP-CPI was more useful to determine the necessity of insulin treatment than F-CPI by means of receiver-operating characteristic curve analysis (unpublished observation). However, the question of why CPI is useful and exactly what it shows has not been fully answered.

Our results have shown that CPI is significantly associated with both the total insulin secretion induced by oral glucose stimulation and the maximum insulin secretion in the glucagon tolerance test, i.e., intravenous non-glucose stimulation, even when F-CPI was measured from a fasting blood sample. This could be because fasting blood glucose levels in patients with type 2 diabetes on the day after admission are high (measured at 138.5 mg/dL on an average), and high levels of insulin are secreted, even in the resting state. In fact, after the diet-tolerance test, a weaker correlation was observed between PP-CPI levels and CPR_6 than between F-CPI and CPR_6. On the other hand, the insulinogenic index obtained from 75g-OGTT is known to decrease during the impaired glucose-tolerance (IGT) stage before the onset of type 2 diabetes [8], which suggests that it has a weak correlation with both F-CPI and PP-CPI, because the index is usually lower than 0.4 in patients diagnosed with type 2 diabetes.

Interestingly, we found a weak but significant negative correlation between F-CPI and HOMA-R^{-1} and between F-CPI and the composite index. Both HOMA-R^{-1} and the composite index represent insulin sensitivity. In contrast, a weaker correlation was observed between PP-CPI and the insulin sensitivity index than between F-CPI and the insulin sensitivity index, although the reason was not clear. This is the first report to reveal the differences in the characteristics of F-CPI and PP-CPI. Our results show that CPI is a total index correlated with insulin secretion and to some extent, insulin sensitivity.

In contrast to our findings, Meier et al. reported that F-CPI was correlated with the pancreatic β-cell area of the resected specimen. However, the authors found that the CPR index, which was calculated from the plasma glucose level measured concomitantly with C-peptide at 15 min after glucose load of 75-g OGTT, showed a strong correlation with the pancreatic β-cell area, which was stronger than that observed with F-CPI [12]. Type 2 diabetes is a progressive disease, and it is thought that the functional β-cell mass begins to decrease before disease onset and decrease along with diabetic duration [13]. Insulin necessity may develop along with the duration of diabetes to compensate for the functional β-cell loss. We further examined the relationship between the duration of type 2 diabetes and CPI. A weak, yet significant, correlation between PP-CPI and the disease duration was observed. In contrast, the correlation between F-CPI and diabetes duration was less evident than the correlation between PP-CPI and disease duration, although the reason was not clear. Nybäck-Nakell et al. also reported that PP-CPI was a useful index for the assessment of β-cell function, because it decreased with the duration of diabetes [14]. However, it might be difficult to precisely determine the disease duration from asymptomatic patients with type 2 diabetes. Therefore, we examined the relationship between PP-CPI and the degree of diabetic retinopathy, which is thought to be partially dependent on genetic factors, and the pathogenesis of which is considered to be related to the duration of hyperglycemic exposure [15-16]. It was revealed that PP-CPI decreases with the degree of diabetic retinopathy, which in turn, confirmed the correlation with the disease duration.

In summary, the CPR indices are clinically useful because they are correlated with insulin secretion capacity. However, they are also the indices that best reflect impaired glucose tolerance, reflecting both insulin sensitivity and disease duration. These indices can therefore be used in medical practice to determine a patient's need for insulin therapy, and thus, they can be used to guide the most appropriate treatment for type 2 diabetes.

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