Analysis of factors influencing postprandial C-peptide levels in Japanese patients with type 2 diabetes: Comparison with C-peptide levels after glucagon load

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ABSTRACT

Aims/Introduction: Postprandial serum C-peptide levels are readily determined in clinical practice and have a good correlation with serum C-peptide levels after glucagon load; the measurement is often used as an index of endogenous insulin secretion. However, the factors affecting postprandial serum C-peptide levels remain to be evaluated.

Materials and Methods: To investigate the clinical factors affecting postprandial serum C-peptide, 2-h postprandial C-peptide levels after breakfast (PPCPR) were analyzed retrospectively for comparison with glucagon-stimulated C-peptide (CPR-6min) levels measured during hospital admission in 273 Japanese patients with type 2 diabetes.

Results: Multiple regression analysis showed that years from diagnosis, body mass index (BMI) and HbA1c were the major independent variables predicting PPCPR ($R^2 = 0.315$). HbA1c was a major factor predicting PPCPR, but did not predict CPR-6min. In addition, HbA1c was negatively correlated with PPCPR ($r = -0.410, P < 0.0001$) and PPCPR/CPR-6min ($r = -0.313, P < 0.0001$).

Conclusions: PPCPR was correlated with common factors predicting CPR, including years from diagnosis and BMI, but also was negatively correlated with HbA1c, a unique factor. These results show that chronic elevation of the glucose level might impair endogenous insulin secretion after meal load, but might have little effect on endogenous insulin secretion after glucagon load. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00126.x, 2011)

KEY WORDS: C-peptide, Meal load, HbA1c

INTRODUCTION

Type 2 diabetes is a heterogeneous disease characterized by insulin resistance and defective insulin secretion1, and is progressive in that the mode of therapy must be altered over the decades of diabetes; diet and exercise therapy alone might be adequate initially, but secondary oral hypoglycemic agent (OHA) treatment and insulin treatment are eventually required2,3. This is, at least in part, as a result of progressive loss of pancreatic β-cell function. The results of the United Kingdom Progressive Diabetes Study (UKPDS) show that pancreatic β-cell function (%β), assessed by Homeostasis Model Assessment (HOMA) in patients allocated to diet or OHA decreased approximately 25% in 5 years4. In addition, a decline in endogenous insulin secretion over more than several decades of diabetes in patients including insulin-treated patients was observed in a cross-sectional study5.

Determination of fasting serum C-peptide level and stimulated serum C-peptide level by intravenous glucagon is used widely to assess endogenous insulin secretory reserves6–9, and the utility of the indices using C-peptide level in choosing insulin therapy has been shown10. The postprandial serum C-peptide level can easily be measured in clinical practice and has a good correlation with the serum C-peptide level after glucagon load11; it is often used as an index of endogenous insulin secretion, and can be used for both non-insulin-treated and insulin-treated patients11–13. Duration of diabetes and body mass index (BMI) are the major factors in serum fasting and glucagon-stimulated C-peptide levels6–10, but the factors affecting postprandial serum C-peptide levels remain to be evaluated.

In the present study of Japanese patients with type 2 diabetes, to evaluate the clinical factors affecting postprandial serum C-peptide by cross-sectional study, 2-h postprandial C-peptide levels after breakfast were analyzed and compared with glucagon-stimulated C-peptide levels.
SUBJECTS AND METHODS

Subjects
A total of 388 Japanese patients with type 2 diabetes who were admitted to Kyoto University Hospital between 1997 and 2002 for poor glycemic control were enrolled in the study. Patients with pancreatic or liver disease, taking diabetogenic medications, pregnant or with serum creatinine ≥1.3 mg/dL, were excluded from the study. Type 2 diabetes mellitus was diagnosed based on the criteria of the American Diabetes Association (ADA)\(^1\). Patients with serum creatinine ≥1.3 mg/dL were excluded, as serum C-peptide immunoreactivity (CPR) is elevated by decreased renal function\(^1\). Of these patients, 115 were excluded as a result of incomplete clinical examinations and the remaining 273 patients, including patients without diabetc medication, oral hypoglycemic agent-treated patients and insulin-treated patients, were analyzed. The clinical profiles of the patients are shown in Table 1.

Methods
On the first day in hospital, medical history, physical examination and laboratory evaluation including glycosylated hemoglobin were carried out. HbA1c was measured using high performance liquid chromatography (HA-8180; Arcray, Kyoto, Japan). The HbA1c (%) value was estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent (%) calculated by the formula HbA1c (%) = HbA1c (Japan Diabetes Society [JDS]) (%) + 0.4%, considering the relational expression of HbA1c (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA1c (NGSP)\(^2\). β-Cell function was evaluated within 1 week after an overnight fast by measuring fasting CPR (FCPR), CPR 6 min after intravenous injection of 1 mg glucagon (CPR-6min)\(^3\) and postprandial CPR. Serum CPR was measured by radioimmunoassay (Daiichi III; Daiichi Radioisotope Laboratories, Osaka, Japan). Postprandial CPR 2 h after breakfast (PPCPR) was determined. The meal at breakfast was prescribed as nutritional therapy according to the treatment guide for diabetes of the JDS\(^4\), which included 516.6 ± 67.7 kcal (mean ± SD) energy consisting of 49% carbohydrate, 16% protein and 35% fat. In patients taking OHA, medication was stopped for measurement of CPR, but was maintained until 1 day before to prevent hyperglycemia during the test\(^5\). Plasma glucose was measured by the glucose oxidase method.

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 Inc., Cary, NC, USA). Data are presented as mean ± SD, unless otherwise noted. The relationship between the parametric clinical data and CPR values was investigated by Pearson’s analysis. The relationship between the non-parametric clinical data and CPR values was investigated by Spearman’s analysis. Clinical parameters among three groups were compared by analysis of variance (ANOVA). For comparison of two groups, Scheffe’s test was carried out. P-values < 0.05 were considered statistically significant.

RESULTS
Simple correlation coefficients between FCPR, CPR-6min and PPCPR, and measures of variables (age, years from diagnosis, sex, BMI, systolic and diastolic blood pressure, HbA1c, serum creatinine and plasma glucose [PG]) were calculated and are shown in Table 2. Years from diagnosis and BMI were significantly correlated with PPCPR, but not with CPR-6min (Figure 1).

Stepwise multiple regression analysis was carried out using the independent variables in Table 2 to predict CPR as a dependent variable (Table 3). FCPR was independently predicted by years from diagnosis, BMI and serum creatinine, accounting for 22.4% of the variability of FCPR. CPR-6min was independently predicted by years from diagnosis and BMI, accounting for 17.9% of the variability of the dependent variables. PPCPR was independently predicted by years from diagnosis, BMI and HbA1c, accounting for 31.5% of the variability of the dependent variables. Thus, HbA1c is an important independent variable predicting PPCPR, but not FCPR or CPR-6min.

Because HbA1c might be involved in decreased PPCPR, the clinical data among three groups of increased HbA1c (≥8.5%, 8.6–10.3%, ≥10.4%) were compared, as shown in Table 4. Although there was no significant difference among these groups in FCPR and CPR-6min, PPCPR was significantly reduced with increasing levels of HbA1c. CPR-6min was significantly correlated with PPCPR (P < 0.0001, r = 0.564, PPCPR = 0.774 × CPR-6min + 1.913; Figure 2a). PPCPR was correlated with CPR-6min in each tertile group of HbA1c (HbA1c ≤ 8.5%...
In the present study, HbA1c was negatively correlated with PPCPR, but not with FCPR or CPR-6min, which suggests that chronic elevation of the glucose level might impair endogenous insulin secretion after a meal load.

Although meal load is not equivalent to glucose load, as it contains nutrients other than carbohydrates that modulate glucose-induced insulin secretion, elevated glucose in plasma might play an important role in meal-stimulated insulin secretion. Indeed, the plasma glucose level after a meal load was increased considerably to more than 100 mg/dL in average. In contrast, the increment of glucose after glucagon load was only approximately 15 mg/dL, indicating a small contribution of glucose elevation to increased insulin secretion by glucagon loading.

**DISCUSSION**

In the present study, HbA1c was negatively correlated with PPCPR, but not with FCPR or CPR-6min, which suggests that chronic elevation of the glucose level might impair endogenous insulin secretion after a meal load.

Because HbA1c was positively correlated with PPG in the present study (P < 0.0001, r = 0.570), HbA1c reflects postprandial glucose level. In simple correlation, both HbA1c and PPG were significantly correlated with PPCPR; whereas in stepwise regression analysis, HbA1c was important to predict PPCPR, but PPG was not. In addition, in simple correlation to PPCPR, the r-value for HbA1c (0.410) was larger compared with that for PPG (0.285; Table 2). These results show that PPCPR is more strongly affected by chronic elevation of glucose levels than by transient elevation of glucose levels.

Multiple regression analysis showed that years from diagnosis, BMI and HbA1c were the major independent variables predicting PPCPR. This shows that years from diagnosis and BMI are common major factors predicting CPR. In contrast, HbA1c was the major factor predicting PPCPR, but not FCPR or CPR-6min, and was negatively correlated with PPCPR. We hypothesized that CPR-6min reflects reserve capacity of endogenous insulin secretion independent of glycemic control and that PPCPR is predicted by a fundamental factor independent of glycemic control and by a variable factor dependent of glycemic control. CPR-6min predicted 31.8% of the variability of PPCPR as shown in Figure 2a. When a regression model using CPR-6min

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**Table 2 | P-values and r-values of correlation between C-peptide immunoreactivity and measures of variables**

| Age (years) | 0.4257 (ND) | 0.0456 (0.121) | 0.3896 (ND) |
| Years from diagnosis | 0.0024 (<0.182) | <0.0001 (<0.246) | <0.0007 (<0.205) |
| Sex | 0.0709 (ND) | 0.1879 (ND) | 0.8321 (ND) |
| BMI (kg/m²) | <0.0001 (0.435) | <0.0001 (0.367) | <0.0001 (0.311) |
| Systolic blood pressure (mmHg) | 0.5551 (ND) | 0.9388 (ND) | 0.0865 (ND) |
| Diastolic blood pressure (mmHg) | 0.5739 (ND) | 0.0327 (0.130) | 0.0705 (ND) |
| HbA1c (%) | 0.0443 (<0.122) | 0.1507 (ND) | <0.0001 (<0.410) |
| sCre (mg/dL) | 0.0104 (0.155) | 0.1641 (ND) | 0.0140 (0.148) |
| FPG (mg/dL) | 0.3764 (ND) | ND | ND |
| PG-6min (mg/dL) | ND | 0.7333 (ND) | ND |
| PPPG (mg/dL) | ND | ND | <0.0001 (<0.285) |

All correlations except correlations between sex and C-peptide immunoreactivity (CPR) were analyzed by Pearson’s analysis. Correlations between sex and CPR were analyzed by Spearman’s analysis. *P*-values are shown. In parenthesis, *r*-values are shown.

**C-peptide after meal load**

![Figure 1](image)

**Figure 1** The relationship between HbA1c and (a) C-peptide immunoreactivity 6 min after intravenous injection of 1 mg glucagon (CPR-6min) and (b) 2-h postprandial C-peptide levels after breakfast (PPCPR).
Data are presented as mean ± SE. BMI, body mass index; CPR-6min, C-peptide immunoreactivity 6 min postprandial plasma glucose; SBP, systolic blood pressure; sCre, serum creatinine; FPG, fasting plasma glucose; PG-6min, plasma glucose 6 min after glucagon load; PPCPR, postprandial CPR; FCPR, fasting CPR; PPPG, postprandial plasma glucose; DBP, diastolic blood pressure; CPR-6min (ng/mL) and HbA1c (%) as independent variables to predict PPCPR as a dependent variable was used, CPR-6min and HbA1c predicted 44.9% of the variability of PPCPR (P < 0.0001, R = 0.670, PPCPR = 6.286 + 0.730 × CPR-6min − 0.434 × HbA1c). The addition of HbA1c as an independent variable increased the prediction of the variability of PPCPR by 13.1%. In the present study, PPCPR/CPR-6min was used as a putative index of variability dependent of glycemic control and was found to be correlated with HbA1c in the present study (Figure 2b). Furthermore, improvement of glycemic control by treatment ameliorates the CPR response after oral glucose load19–21. In addition, the CPR response after glucagon load is affected little with the CPR response after oral glucose load before treatment, whereas it is well-correlated with improved CPR response after oral glucose load after treatment21. Reversible impairment of endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic hyperglycemia deteriorates endogenous insulin response after glucose load is explained by glucose toxicity, in which chronic 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level shown by high HbA1c might impair endogenous insulin secretion after meal load, but has little effect on endogenous insulin secretion after glucagon load. The lack of influence of HbA1c on CPR-6min might be helpful to evaluate reserve capacity of endogenous insulin secretion, even when glycemic control is poor enough to deteriorate postprandial insulin secretion. In contrast, PPCPR is affected by HbA1c and might reflect the state of deteriorated insulin secretion by glucose toxicity that may be recovered by improved glycemic control.

In stepwise regression analysis, HbA1c was not important to predict FCPR, but was important to predict PPCPR. In simple correlation, HbA1c was significantly negatively correlated not only with PPCPR, but also with FCPR, whereas the P-value and r-value for FCPR were larger and smaller, respectively, compared with those for PPCPR (Table 2). Taken together, these findings suggest that glucose toxicity might deteriorate not only postprandial insulin secretion, but also fasting insulin secretion, whereas postprandial insulin secretion might be more vulnerable to glucose toxicity than to fasting insulin secretion.

The suppressive effect of glucose toxicity on insulin secretion in vivo might be attributable to impairment of β-cell responsiveness to glucose and to impairment of incretin effect. However, it is important to understand why glucagon-stimulated CPR is preserved despite severe impairment of glucose-stimulated CPR before treatment to improve hyperglycemia. This remains largely unknown, but our hypothesis based on an in vitro study is that deteriorated intracellular glucose metabolism plays an important role in impaired glucose-induced insulin secretion and that increased intracellular cyclic adenosine 3’,5’-monophosphate concentration derived from glucagon stimulation ameliorates impaired intracellular glucose metabolism to improve suppressed insulin secretion.

A recent study showed that indices using CPR correlate well with β-cell mass by analysis of β-cell areas of samples obtained during pancreatectomy and serum levels of CPR before operation. Thus, PPCPR might reflect not only β-cell mass, but also reversible impairment of endogenous secretion as a result of chronic glucose elevation.

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