Casual C peptide index: Predicting the subsequent need for insulin therapy in outpatients with type 2 diabetes under primary care

Ryota Uehara | Eijiro Yamada | Yasuyo Nakajima | Aya Osaki | Shuichi Okada | Masanobu Yamada

Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, Maebashi, Japan

Correspondence
Eijiro Yamada, Department of Medicine and Molecular Science, Gunma University Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan.
Email: eijiro.yamada@gunma-u.ac.jp

Abstract
Background: Evaluation of residual beta cell function is indispensable in patients with type 2 diabetes as it informs not only diagnoses but also appropriate treatment modalities. However, there is a lack of convenient biomarkers for residual beta cell function. Therefore, we evaluated endogenous insulin level as a biomarker in outpatients who were being treated with insulin therapy and in patients who were introduced to insulin therapy after 4 years.

Methods: Data of 174 outpatients with type 2 diabetes (50% male) whose glycemia was moderately controlled (glycated A1c 7.3% [5.2%–14.8%]) were reviewed. Twenty patients whose estimated glomerular filtration rate was lower than 30 ml/min/1.73 m² were excluded from the evaluation of endogenous insulin level with both casual C-peptide index (C-CPI) and urinary C-peptide/creatinine ratio (determined at any time, generally 1–2 h after breakfast). Patients were stratified based on the provision of insulin therapy.

Results: C-CPI and UCPCR were significantly lower in the insulin-treated patients than in the insulin-untreated patients (0.9 vs. 2.2, \(p < 0.0001\); 24.7 vs. 75.5, \(p = 0.0003\), respectively). Moreover, C-CPI were significantly lower in the insulin-requiring patients for 4 years than in the insulin-unrequiring patients (1.0 vs. 1.7, \(p = 0.0184\)). The multivariate logistic regression analysis revealed that both indicators of insulin secretion influenced the requirement for insulin therapy, but C-CPI could serve as the most convenient and useful biomarker for not only current insulin therapy requirements (\(p = 0.0002\)) but also the subsequent requirement for insulin therapy (\(p = 0.0008\)).

Conclusions: C-CPI could be determined easily, and it was found to be a more practical marker for outpatients; therefore, our findings would have critical implications for primary care.

Keywords
casual examination, C-peptide index, type 2 diabetes, urinary C-peptide/creatinine ratio

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. Journal of Diabetes published by Ruijin Hospital, Shanghai JiaoTong University School of Medicine and John Wiley & Sons Australia, Ltd.
Highlights:
- Analyses of the factors affecting insulin introduction in the 4-year period from 2016 and 2020 were conducted. Multivariate logistic regression analysis revealed that C-CPI contributed the most. The C-CPI may serve as a convenient useful biomarker for not only the requirement current insulin treatment but also the requirement of insulin therapy for 4 years.
- C-CPI could be determined easily.
- It can be a convenient biomarker for predicting the requirement for insulin therapy.

1 | INTRODUCTION

Type 2 diabetes is characterized by insulin resistance and deficient insulin secretion, although it does not develop only in response to insulin resistance.1,2 Insulin resistance necessitates more insulin to maintain blood glucose; therefore, not only the number of pancreatic beta cells but also insulin production per cell must be increased to compensate for this deficit.3 This continued load on beta cells may lead to apoptotic cell death and the development of diabetes.1,3,4 In this respect, the residual function of pancreatic beta cells may already be approximately 50% of the normal level during diabetes development.5 After the development of diabetes, this load may result in a progressive decline in pancreatic beta cell function, thereby necessitating insulin therapy. Therefore, evaluation of residual insulin secretion during the course of type 2 diabetes is important when choosing between insulin therapy and other treatments, as diabetes is a lifelong condition.1,4,6 Relevant research is of clinical significance for the development of new therapies aimed at improving insulin secretion.4,7

C-peptide immunoreactivity (CPR) is commonly used to evaluate endogenous insulin level. Insulin is generated upon the enzymatic cleavage of its precursor, proinsulin, in pancreatic beta cells and is subsequently secreted into the blood (both insulin and CPR are secreted in equal amounts).8,9 Although the insulin concentration can be measured using immunoassays, it is often unstable, resulting in inconsistent measurements.10 Moreover, insulin concentration can be measured, but exogenous and endogenous insulin cannot be distinguished in patients on insulin therapy. However, unlike insulin, the physiological function of CPR for improved glycemic control in diabetes is still controversial.8,9 CPR is more stable than insulin; therefore, CPR level is evaluated more commonly to predict the need for insulin therapy.11,12 It is important to evaluate the CPR level adjusted to blood glucose level to evaluate the function of residual pancreatic beta cells. In this respect, determining the CPR index (C-peptide index [CPI]), that is, fasting serum CPR (ng/ml)/fasting blood glucose (mg/dl) \times 100, is considered an appropriate approach.8,11,13 The CPI is widely used to assess endogenous insulin secretory reserves in both type 1 and type 2 diabetes. Moreover, it could be the indicator for insulin requirements for appropriate glycemic control in type 2 diabetes.11-13

Although the CPI can be used as a factor to evaluate the function of residual pancreatic beta cells, its normal range is determined when fasting.11,13 Considering that most patients with type 2 diabetes are managed via primary care, it is often difficult to check the blood of all patients while they are fasting. Moreover, the CPI during fasting might not reflect the additional secretion of insulin as a result of food intake, and this is also important when evaluating the function of residual pancreatic beta cells. Therefore, measurement of the casual CPI (C-CPI) in outpatients at any time may prove to be more efficient; however, to date, only a few studies have investigated the applicability of the C-CPI in outpatients. Additionally, the use of the urinary C-peptide/creatinine ratio (UCPCR) has been reported as a noninvasive and convenient new marker for insulin secretion.14,15 However, serum CPR is restricted to the hospital setting and requires serum separation by centrifugation and subsequent freezing; in contrast, the UCPCR is stable at room temperature for up to 3 days.15 Importantly, the correlation between serum CPR and UCPCR has not yet been fully evaluated.

In the present study, we reassessed the characteristics of Japanese outpatients with type 2 diabetes requiring insulin therapy by measuring the C-CPI and UCPCR to identify the requirement for insulin therapy. We also examined the characteristics of outpatients with type 2 diabetes requiring insulin therapy after 4 years, which, to the best of our knowledge, is the longest observational period in such studies.
2 | METHODS

2.1 | Ethics statement

This study was approved by the Gunma University Institutional Review Board and conformed to the tenets of the Declaration of Helsinki (revised in Fortaleza, Brazil; October 2013). All patients provided written informed consent before undergoing any study-related procedures.

2.2 | Subjects

The data of all outpatients with type 2 diabetes visiting the Division of Endocrinology and Diabetes, Keiaido Hospital, were reviewed, and patients whose CPR was measured in 2016 were selected. Patients whose estimated glomerular filtration rate (eGFR) was lower than 30 ml/min/1.73 m² were excluded as the CPR in them would be unstable and inaccurate.16

2.3 | Measurements

Endogenous insulin concentration was estimated by measuring the casual serum CPR level, casual blood glucose, or UCPCR evaluated at any time point during the visit (normally up to 1–2 h after breakfast). Both serum and urine CPR levels (ng/ml) were examined using the chemiluminescent immunoassay with the ARCHITECT i2000SR immunoassay analyzer (Abbot Japan) by LSI Medience Corporation, Inc. (Tokyo, Japan). The C-CPI was calculated using the following equation: casual serum CPR (ng/ml)/casual blood glucose (mg/dl) × 100.

2.4 | Statistical analysis

Data are presented as median (range) and percentage for frequency variables. Results are expressed as the average value for continuous variables or as value and percentage for categorical variables. Group comparisons were performed using the analysis of variance and Wilcoxon rank-sum test for continuous variables without normal distribution. The variables found to be significant in the univariate analysis (p < .15) were included in the multivariate models. Associations between continuous variables were examined using Spearman’s correlation coefficient analysis. All tests of significance and the resulting p values were two sided, and the level of significance was set at 5%. The statistical analyses were performed using JMP Pro 15.2.0 software (SAS Institute, Cary, NC, USA).

3 | RESULTS

We screened 174 outpatients with type 2 diabetes (50% male) whose glycemia was moderately controlled (glycated HbA1c 7.3% [5.2%–14.8%]). The characteristics of the 174 patients are presented in Table 1. Twenty patients with the eGFR lower than 30 ml/min/1.73 m² were excluded from the evaluation endogenous insulin levels with both C-CPI and UCPCR. Profiles of all 154 enrolled patients are provided in Table 2A and B. The median age of the patients was 71.0 years, and 48.4% of the patients were male; the median duration of diabetes was 13.0 years. We evaluated the correlation of C-CPI and UCPCR with sex and confirmed that the relationships were similar (data not shown). In 2016, the median body mass index of the patients was 23.9 kg/m², which significantly decreased in 2020 (23.8 kg/m², p = .0188). Although the glycated hemoglobin (HbA1c) level and eGFR did not significantly change from the baseline, the urine albumin creatinine ratio significantly increased (11.6 vs. 17.4 mg/g Cr, p = .0353; Table 2B). Similarly, the C-CPI significantly increased in 2020 compared with that in 2016 (Table 2B).
With respect to the treatment type, whereas the usage of sulfonylurea in 2020 decreased by approximately 4% compared to that in 2016, that of glinide/biguanide and sodium glucose cotransporter 2 (SGLT2) inhibitors in 2020 increased by more than 5% compared to that in 2016. In particular, the use of SGLT2 inhibitors in 2020 increased two-fold compared to that in 2016, as there was evidence that these agents prevented the occurrence of cardiovascular events.\textsuperscript{17} Whereas the usage of dipeptidyl peptidase 4 (DPP4) inhibitors decreased, that of glucagon-like peptide-1 (GLP-1) in 2020 analogs increased compared to that in 2016, partially because they both are incretins and cannot be administrated simultaneously to patients in Japan.\textsuperscript{18}

We first observed the determinant for the current insulin therapy. Table 3 summarizes the baseline characteristics of the insulin-untreated and -treated patients. Although there was no significant difference in the age of patients between the two groups, the duration of diabetes in the insulin-treated patients was significantly longer than that in the insulin-untreated patients (12.0 vs. 17.5 years, \(p = .0006\)). Furthermore, the HbA1c level was significantly higher in the insulin-treated patients than in the insulin-untreated patients (7.9% [62 mmol/mol] vs. 7.2% [55 mmol/mol], \(p < .0001\)). More importantly, both C-CPI and UCPCR were significantly lower in the insulin-treated patients than in the insulin-untreated patients (0.9 vs. 2.2, \(p < .0001\); 24.7 vs. 75.5, \(p = .0003\), respectively; Table 3). The multivariate logistic regression analysis revealed that the diabetes duration in patients did not significantly differ between the groups. The HbA1c level, C-CPI, and UCPCR exhibited a significant difference between the groups; the most significant difference was in C-CPI (\(p = .0002\)). The cutoff of C-CPI was 1.45 for the insulin-treated group (area under the curve = 0.85241, sensitivity 85.0%, sensitivity 71.9%; data not shown).

Next, we retrospectively examined the characteristics of patients who were introduced to insulin therapy after 4 years. Among the 154 patients, 116 who did not use insulin in 2016 were reevaluated, and 6 patients required insulin therapy. Table 4 presents the characteristics of the insulin-untreated and insulin-introduced patients; only the C-CPI and the number of patients receiving GLP-1 analogs significantly differed between the groups. Importantly, multivariate logistic regression analysis revealed that although treatment with both C-CPI and GLP-1 analogs contributed to the introduction of insulin, C-CPI contributed the most (\(p = .0008\); Table 4). The cutoff of C-CPI was 1.45 for the patients to be introduced to insulin therapy (area under the curve = 0.82652, sensitivity 100.0%, sensitivity 63.6%; data not shown).

Finally, we investigated the factors associated with the change in CPI (\(\Delta\text{CPI}\)) for 4 years (Table 5) and found that the HbA1c level, C-CPI, and usage of DPP4 inhibitors and glinide/biguanide positively correlated with \(\Delta\text{CPI}\). Interestingly, the multivariate logistic regression analysis revealed that the use of DPP4 inhibitors contributed the most to the unchanged CPI (Table 5).
DISCUSSION

Residual beta cell function is indispensable in patients with type 2 diabetes because it informs not only diagnoses but also the treatment itself.16,19 Moreover, the function of pancreatic beta cells in patients with type 2 diabetes decreases gradually. However, patients with type 1 diabetes, who have a low endogenous insulin level, may experience more glucose fluctuation, thus making the patient more susceptible to reduced quality of life and complications of diabetes.20 Assessment of residual beta cell function at any time point would enable a more accurate assessment of pancreatic beta cell function, which will guide not only current therapeutic decisions but also future decisions.

To assess residual pancreatic beta cell function, we first examined factors contributing to current insulin therapy and insulin introduction in the 4-year period from 2016 and 2020. The results are summarized in Tables 3 and 4.

### Table 3
Analyses of the factors used for determining current insulin therapy. A total of 154 patients were examined to compare the patients who used insulin and those who did not in 2020. Group comparisons were performed as described in the Methods.

| Insulin therapy (2020) | No, median (range) | Yes, median (range) | Univariate p | Multivariate p |
|-----------------------|--------------------|---------------------|--------------|---------------|
| N                     | 114                | 40                  | –            | –             |
| Sex (% male)          | 45.6               | 55.0                | .3067        | –             |
| Age (years)           | 70.0 (43–89)       | 73.5 (33–89)        | .7276        | –             |
| Duration of diabetes (years) | 12.0 (6–28) | 17.5 (7–32) | .0006* | 0.594 |
| Body mass index (kg/m²) | 24.1 (15–36.7) | 23.3 (15.4–2.9) | .1074* | .5365 |
| HbA1c (%)             | 7.2 (5.5–10.5)     | 7.9 (6–14.8)        | <.0001*      | .0009*        |
| eGFR (ml/min/1.73 m²) | 67.0 (33.1–122.0) | 72.2 (31.3–136.7)   | .3828        | –             |
| UACR (mg/g Cr)        | 16.9 (1.7–1275.1)  | 23.4 (1.6–9722.4)   | .0501*       | .1600         |
| C-CPI                 | 2.2 (0.5–8.8)      | 0.9 (0.2–3.57)      | <.0001*      | .0002*        |
| UCPCR (mg/g Cr)       | 75.5 (9.3–465.6)   | 24.7 (2.5–191.0)    | .0003*       | .0301*        |

Abbreviations: C-CPI, casual C-peptide index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; UACR, urine albumin creatine ratio; UCPCR, urine C-peptide-to-creatinine ratio.

### Table 4
Analyses of the factors affecting insulin introduction in the 4-year period from 2016 and 2020. A total of 116 patients who had not used insulin in 2016 were examined to compare the patients who used insulin and those who did not in 2020. Group comparisons were performed as described in the Methods.

| Insulin introduction | No, median (range) | Yes, median (range) | Univariate p | Multivariate p |
|----------------------|--------------------|---------------------|--------------|---------------|
| N                    | 110                | 6                   | –            | –             |
| Sex (% male)         | 47.3               | 33.3                | .5050        | –             |
| Age (years)          | 66 (39–85)         | 58 (29–75)          | .0629*       | .3540         |
| Duration of diabetes (years) | 8.5 (2–24) | 12 (4–20) | .5649 | – |
| Body mass index (kg/m²) | 24.5 (16.6–37.4) | 22.7 (19.6–30.8) | .8344 | – |
| HbA1c (%)            | 6.9 (5.5–13.5)     | 7.5 (6.8–8.5)       | .1405*       | .3890         |
| eGFR (ml/min/1.73 m²)| 67.6 (37.8–106.7) | 62.1 (52.8–132.2)   | .4294        | –             |
| UACR (mg/g Cr)       | 11.0 (0–815.4)     | 11.3 (2.4–17.4)     | .5192        | –             |
| C-CPI                | 1.7 (0.3–4.4)      | 1.0 (0.4–1.5)       | .0184*       | .0008*        |
| Sulfonylurea (%)     | 20.0               | 50.0                | .0818*       | .3206         |
| Glinide (%)          | 17.3               | 16.7                | .9695        | –             |
| Dipeptidyl peptidase-4 inhibitor (%) | 61.8 | 33.3 | .1648 | – |
| Biguanide (%)        | 43.5               | 50.0                | .7555        | –             |
| α-glucosidase inhibitor (%) | 52.7 | 50.0 | .8963 | – |
| Sodium glucose cotransporter 2 inhibitor (%) | 19.1 | 16.7 | .8827 | – |
| Thiazolidine (%)     | 3.6                | 0.0                 | .6345        | –             |
| Glucagon-like peptide-1 receptor agonist (%) | 7.3 | 33.3 | .0268* | .0056* |

Abbreviations: C-CPI, casual C-peptide index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; UACR, urine albumin creatine ratio; UCPCR, urine C-peptide-to-creatinine ratio.
analyses of the factors used for determining the patients. Furthermore, in the current study, all test samples were collected at random time points depending on the availability of the patients. Considering that serum CPR and urine CPR are metabolized differently, the time of testing is a critical component for accurate assessment. Our study indicated that at the time points when outpatients were tested, the C-CPI was a more predictable marker than the UCPCR for insulin therapy.

Determining the changes in the C-CPI might be necessary in the evaluation of other aspects in the future, as it can reveal the effect of current treatments on beta cell function. Here, we examined the factors associated with ΔC-CPI over 4 years, demonstrating that the use of DPP4 inhibitors was most strongly correlated (except the initial C-CPI). In fact, the findings of several basic science studies and clinical data have suggested that DPP4 inhibitors can preserve pancreatic beta cell function. Specifically, DPP4 inhibitors have been shown to mitigate endoplasmic reticulum stress, which often occurs in the beta cells of patients with diabetes, while also aiding in insulin production to compensate for this stress. Our results are consistent with this finding, and they indicate that ΔC-CPI can serve as a critical biomarker for future therapy of type 2 diabetes.

When interpreting the current findings, several limitations have to be considered. We examined only “casual” tests for serum and urine, which may be affected by other conditions, such as the time of food intake before sample collection. In this respect, additional indices such as acute insulin response (AIR), AIRmax, and glucagon testing should be considered to evaluate residual insulin secretion. Additionally, this study involved a retrospective cross-sectional design, had a small number of patients, and was performed in only a single hospital. Thus, the demographics of our patients may differ from those at other hospitals in Japan, particularly with respect to treatment. Although the present study included a longitudinal follow-up of 4 years, a cause-and-effect relationship could not be discerned.

In conclusion, we reassessed the biomarkers to examine the function of pancreatic beta cells in type 2 diabetes and found that C-CPI may serve as a convenient useful biomarker for not only the requirement current insulin treatment but also the requirement of insulin therapy for 4 years. Interestingly, we also observed that DPP4 inhibitors, which have been reported to preserve pancreatic beta cell function, were most strongly correlated with the changes in the C-CPI, supporting the assumption that the C-CPI can be used as a biomarker to examine the function of pancreatic beta cells. The C-CPI could be determined easily and was found to be a more practical marker for outpatients; therefore, the present study results could have critical implications for primary care. Nevertheless, further studies are required with larger cohorts to confirm our conclusions regarding the strategy for insulin therapy.

| ΔCPI (N = 154) | Univariate | Multivariate |
|----------------|------------|--------------|
|                | p          | p            |
| Sex (% male)   | .4469      | –            |
| Age (years)    | .4481      | –            |
| Duration diabetes mellitus (years) | .5216 | – |
| Body mass index (kg/m²) | .6680 | – |
| HbA1c (%)      | .0287*     | .5514        |
| eGFR (ml/min/1.73 m²) | .6833 | – |
| UACR (mg/g Cr) | .6549      | –            |
| C-CPI          | .0007*     | .0074*       |
| Sulfonylurea (%) | .6072     | –            |
| Glinide (%)    | .4916      | –            |
| Dipeptidyl peptidase-4 inhibitor (%) | .0003* | .0010* |
| Biguanide (%)  | .0335*     | .8350        |
| α-glucosidase inhibitor (%) | .3778 | – |
| Sodium glucose cotransporter 2 inhibitor (%) | .7126 | – |
| Thiazolidine (%) | .2890 | – |
| Glucagon-like peptide-1 receptor agonist (%) | .1014* | .0526 |
| Insulin (%)    | .5538      | –            |

Abbreviations: C-CPI, casual C-peptide index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; UACR, urine albumin creatine ratio.
DISCLOSURE

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ACKNOWLEDGEMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID

Eijiro Yamada https://orcid.org/0000-0002-0332-8605
Shuichi Okada https://orcid.org/0000-0003-1403-6840

REFERENCES

1. Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58:773-795.
2. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005;26:19-39.
3. Brandon BB, Christopher JR, Joseph SG. The dynamic plasticity of insulin production in β-cells. Mol Metab. 2017;6:958-973.
4. Rojas J, Bermudez V, Palmar J, et al. Pancreatic beta cell death: novel potential mechanisms in diabetes therapy. J Diabetes Res. 2018;2018:9601801. doi:10.1155/2018/9601801
5. Marrif HI, Al-Sounousi SI. Pancreatic β cell mass death. Front Pharmacol. 2016;7:83.
6. Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. Diabetes Care. 2009;32(Suppl 2):S253-S259. doi:10.2337/dc09-s318
7. Kathleen A, Reisman T. Interventions to preserve beta-cell function in the management and prevention of type 2 diabetes. Curr Diab Rep. 2013;13:252-260.
8. Torn C. C-peptide and autoimmune markers in diabetes. Clin Lab. 2003;49:1-10.
9. Rubenstein AH, Clark JL, Melani F, Steiner DF. Secretion of proinsulin C-peptide by pancreatic β cells and its circulation in blood. Nature. 1969;224:697-699.
10. Marcovina S, Bowsher RR, Miller WG, et al. Insulin Standardization Workgroup. Standardization of insulin immunoassays: report of the American Diabetes Association Workgroup. Clin Chem. 2007;53:711-716.
11. Funakoshi S, Fujimoto S, Hamasaki A, et al. Utility of indices using C-peptide levels for indication of insulin therapy to achieve good glycemic control in Japanese patients with type 2 diabetes. J Diabetes Invest. 2011;2:297-303.
12. Andrade RLM, Gigante DP, de Oliveira IO, Horta BL. C-peptide and cardiovascular risk factors among young adults in a southern Brazilian cohort. BMC Endor Disord. 2018;18:80.
13. Asano T, Kawamura M, Watanabe T, et al. Indices of urinary and serum C-peptide corrected with fasting plasma glucose for decision-making of insulin therapy in type 2 diabetes-validation and comparison. J Japan Diabetes Soc. 2008;51:759-763.
14. Elzahar W, Arafa A, Youssef A, Erfan A, el Amrousy D. Urinary C-peptide creatinine ratio to differentiate type 2 diabetes mellitus from type 1 in pediatric patients. Eur J Pediatr. 2020;179:1115-1120.
15. McDonald TJ, Knight BA, Shields BM, Bowman P, Salzmann MB, Hattersley AT. Stability and reproducibility of a single-sample urinary C-peptide/creatinine ratio and its correlation with 24-h urinary C-peptide. Clin Chem. 2009;55:2035-2039.
16. Thomas NJ, Shields BM, Besser RE, et al. The impact of gender on urine C-peptide creatinine ratio interpretation. Ann Clin Biochem. 2012;49:363-368.
17. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-2128.
18. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696-1705.
19. Yu MG, Keenan HA, Shah HS, et al. Residual β cell function and monogenic variants in long-duration type 1 diabetes patients. J Clin Invest. 2019;129:3252-3263.
20. Bo S, Cavallo-Perin P, Gentile L, Repetti E, Pagano G. Relationship of residual beta-cell function, metabolic control and chronic complications in type 2 diabetes mellitus. Acta Diabetol. 2000;37:125-129.
21. Carlson AL, Criego AB, Martens TW, Bergenstal RM. Hba1c: the glucose management indicator, time in range, and standardization of continuous glucose monitoring reports in clinical practice. Endocrinol Metab Clin North Am. 2020;49:95-107.
22. Gjessing HJ, Matzen LE, Faber OK, Froland A. Fasting plasma C-peptide, glucagon stimulated plasma C-peptide, and urinary C-peptide in relation to clinical type of diabetes. Diabetologia. 1989;32:305-311.
23. Heding LG, Rasmussen SM. Human C-peptide in normal and diabetic subjects. Diabetologia. 1975;11:201-206.
24. Del Prato S, Chilton R. Practical strategies for improving outcomes in T2DM: the potential role of pioglitazone and DPP4 inhibitors. Diabetes Obes Metab. 2018;20:786-799.
25. Shimizu S, Hosooka T, Matsuda T, et al. DPP4 inhibitor vildagliptin preserves β-cell mass through amelioration of endoplasmic reticulum stress in C/EBPβ transgenic mice. J Mol Endocrinol. 2012;49:125-135.
26. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet. 2019;394:1519-1529.
27. Saisho Y. Postprandial C-peptide to glucose ratio as a marker of β cell function: implication for the management of type 2 diabetes. Int J Mol Sci. 2016;19:744.
28. Sun Q, Yue P, Deiliulis JA, et al. Ambient air pollution exaggerates adipose inflammation and insulin resistance in a mouse model of diet-induced obesity. Circulation. 2009;119:538-546.
29. Scheen AJ, Castillo MJ, Lefèbvre PJ. Assessment of residual insulin secretion in diabetic patients using the intravenous glucagon stimulatory test: methodological aspects and clinical applications. Diabetes Metab. 1996;22:397-406.