Proinsulin is sensitive to reflect glucose intolerance

Akinobu Nakamura1*, Hideaki Miyoshi2, Shigekazu Ukawa34, Koshi Nakamura3, Takafumi Nakagawa5, Yasuo Terauchi6, Akiko Tamakoshi3, Tatsuya Atsumi1

1Department of Rheumatology, Endocrinology and Nephrology, 2Division of Diabetes and Obesity, 3Department of Public Health, Faculty of Medicine and Graduate School of Medicine, Hokkaido University Graduate School of Medicine, Sapporo, 4Research Unit of Advanced Interdisciplinary Care Science, Osaka City University Graduate School of Human Life Science, Osaka, 5The Hokkaido Centre for Family Medicine, Sapporo, and 6Department of Endocrinology and Metabolism, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

Keywords
β-Cell function, Epidemiology, Proinsulin

*Correspondence
Akinobu Nakamura
Tel: +81-11-706-5915
Fax: +81-11-706-7710
E-mail address: akinbo@tim.hi-ho.ne.jp

J Diabetes Investig 2020; 11: 75–79
doi: 10.1111/jdi.13106

INTRODUCTION

Previous studies have shown that deterioration of pancreatic β-cell function or mass becomes apparent before a diagnosis of type 2 diabetes1–6. Focusing on the natural history of type 2 diabetes progression, insulin secretion initially increases to compensate for peripheral insulin resistance. However, this increase in insulin secretion represents a relative shortage of insulin, and this impaired β-cell function leads to the development of prediabetes and progression to frank type 2 diabetes5. Taken together, establishment of an evaluation method for estimating β-cell function, which could show a strong association with glucose tolerance, would be expected.

Among several methods for estimating β-cell function, assessment using parameters from fasting blood samples would be simple and clinically useful. However, it has not been clarified which parameters could show a strong association with glucose tolerance. The objective of the present population-based study was to investigate associations between glucose tolerance and β-cell function, as evaluated by five estimation methods, in a general Japanese population.
METHODS

Study participants
In the present cross-sectional study, we analyzed data from the Dynamics of Lifestyle and Neighborhood Community on Health Study (DOSANCO Health Study), as described previously. In short, a total of 545 residents (300 women) in the town of Suttu, Hokkaido, Japan, aged 35–79 years, provided their basic information, including age, sex, medical history, anthropometric measurements and fasting blood samples. Of these 545 participants, those who had missing data on insulin levels (n = 3) or were using antidiabetic agents (n = 53) were excluded. The remaining 489 individuals (263 women) were considered eligible study participants and included in the subsequent analyses. The study design was reviewed by the ethics board of Hokkaido University School of Medicine (15-002 and 17-015), and signed informed consent was obtained from all participants.

Data collection
The weight and height of the participants were measured using a calibrated scale after they had removed their shoes and any heavy clothing. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Venous blood samples were collected at rest in the morning after an overnight fast to measure levels of fasting plasma glucose (FPG), insulin, C-peptide (CPR) and glycated hemoglobin (HbA1c). These parameters were measured using standard techniques. Proinsulin (PI) concentrations (pmol/L) were measured using a radioimmunoassay (Millipore Corporation Inc., Burlington MA, USA).

Statistical analysis
Initially, glucose tolerance was categorized into the following three groups: normal glucose tolerance (NGT), prediabetes (PDM) and diabetes (DM). NGT was defined as FPG <110 mg/dL and HbA1c <5.7%, and PDM was defined as FPG 110–125 mg/dL or HbA1c 5.7–6.4%, or both. Participants were considered to have diabetes if they had a previous history of diabetes, FPG ≥126 mg/dL or HbA1c ≥6.5%. β-Cell function was estimated by homeostasis model assessment of β-cell function (HOMA-%); PI/CPR; C-peptide index (CPI), according to the formula 100 \times \text{fasting} – \text{CPR} / \text{FPG}; ratio of PI-to-CPR (PI/CPR); and ratio of PI-to-insulin (PI/I).

Anthropometric and biochemical characteristics were crudely compared among the three groups regarding glucose tolerance, using one-way analysis of variance, the Kruskal–Wallis test or the χ²-test. Because data on all five parameters of β-cell function showed skewed distributions, the values were normalized by natural logarithmic (ln) transformation. Comparisons of these log-transformed parameters among the groups were assessed by analysis of covariance, followed by Tukey’s honestly significant difference test for multiple post-hoc comparisons. The model incorporated the following covariates: age (years, as a continuous variable), sex (male or female) and BMI (kg/m², as a continuous variable).

Next, to explore a potential marker of early pancreatic β-cell dysfunction, we examined the association between glucose tolerance and β-cell function among participants without diabetes. In this analysis, glucose tolerance was assessed based on HbA1c levels. We compared anthropometric and biochemical characteristics in the participants grouped according to quartiles of HbA1c, using statistical methods the same as those used in the first analysis.

All tests were two-sided, and P < 0.05 was considered statistically significant. Statistical analysis was carried out using JMP 10 (SAS Institute Inc., Cary, NC, USA).

RESULTS
A total of 489 participants (263 women) were divided into three groups: NGT (n = 328), PDM (n = 113) and diabetes (n = 48) groups. Anthropometric and biochemical characteristics of the participants are shown in Table 1. Age, proportion of women, BMI, waist circumference, and levels of insulin and CPR were positively associated with glucose intolerance. Table 2 shows β-cell function, as evaluated by the five estimation methods, for each glucose tolerance group. In the crude analysis (model 1), ln(HOMA-β%) was significantly lower in the diabetes group, but not in the PDM group, compared with the NGT group; ln(CPI) did not differ significantly among the three groups. Compared with the NGT group, ln(PI/I) was significantly higher in the diabetes group, but not in the PDM group. Of note, ln(PI) and ln(CPI)/ln(CPR) were significantly higher in the diabetes group than in the PDM and NGT groups, and these parameters were significantly higher in the PDM group than in the NGT group. Similar results were observed for ln (PI) and ln(PI/CPR) after adjustment for age and sex (model 2). Only ln(PI) in the PDM group was significantly higher compared with that in the NGT group after adjustment for age, sex and BMI (model 3).

As shown in Table 3, age, BMI, waist circumference, and levels of insulin and CPR were positively correlated with HbA1c quartile among the participants without diabetes. In the crude analysis (model 1), ln(PI) and ln(PI/CPR) were significantly and positively associated with HbA1c quartile, and the results were similar after adjustment for age and sex (model 2; Table 4). Only ln(PI) was significantly and positively correlated with HbA1c quartile in participants without diabetes, after adjustment for age, sex and BMI (model 3; Table 4).

DISCUSSION
The present results showed that, of the five estimation methods, fasting PI was the strongest associated with glucose tolerance. Increased PI might be caused by an intrinsic defect in proinsulin processing or an increased secretory demand on β-cells. Indeed, consistent with the present results, fasting PI levels are significantly elevated not only in individuals with diabetes, but also in those with impaired fasting glucose and impaired glucose tolerance compared with those with NGT. Although PI/I and HOMA-β% are known surrogate markers of β-cell dysfunction, we examined the association between glucose tolerance and β-cell function among participants without diabetes. In this analysis, glucose tolerance was assessed based on HbA1c levels. We compared anthropometric and biochemical characteristics in the participants grouped according to quartiles of HbA1c, using statistical methods the same as those used in the first analysis.

All tests were two-sided, and P < 0.05 was considered statistically significant. Statistical analysis was carried out using JMP 10 (SAS Institute Inc., Cary, NC, USA).
Table 1 | Anthropometric and biochemical characteristics of 489 study participants

| Model | Total participants | Glucose tolerance | P-value |
|-------|--------------------|-------------------|---------|
|       | Glucose tolerance  |                   |         |
|       | n                  | NGT group          | PDM group | DM group |
| Age (years) | 489 | 580 ± 125 | 552 ± 127 | 63.7 ± 10.0 | 634 ± 9.9 | <0.001 |
| No. women (%) | 263 (53.8) | 186 (56.7) | 62 (54.9) | 15 (31.3) | 0.004 |
| BMI (kg/m²) | 23.7 ± 3.6 | 23.3 ± 3.4 | 24.4 ± 4.0 | 24.4 ± 3.9 | <0.008 |
| Waist circumference (cm) | 81.6 ± 10.4 | 80.2 ± 9.9 | 83.7 ± 10.7 | 86.3 ± 11.5 | <0.001 |
| FPG (mg/dL) | 93 (86–100) | 90 (84–96) | 99 (92–108) | 128 (112–141) | <0.001 |
| HbA1c (%) | 5.4 (5.2–5.7) | 5.3 (5.1–5.4) | 5.8 (5.7–6.0) | 6.5 (6.0–6.9) | <0.001 |
| Insulin (µU/mL) | 4.3 (2.8–6.5) | 4.0 (2.8–5.8) | 5.2 (2.9–7.3) | 6.0 (4.2–9.9) | <0.001 |
| C-peptide (ng/mL) | 1.2 (0.9–1.7) | 1.1 (0.9–1.5) | 1.4 (1.0–1.9) | 1.8 (1.2–2.5) | <0.001 |

Data are presented for the entire group and for participants grouped by their glucose tolerance. Values are expressed as mean ± standard deviation, median (interquartile range) or the number (%) of participants in that category. One-way analysis of variance, Kruskal-Wallis test or χ²-test were used to compare each parameter among the three glucose tolerance groups. BMI, body mass index; DM, diabetes; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; NGT, normal glucose tolerance; PDM, prediabetes.

Table 2 | β-Cell function evaluated by five estimation methods

| Model | Glucose tolerance | P value |
|-------|-------------------|---------|
|       | NGT group          | PDM group | DM group |
| In (HOMA-β%) | 4.00 (3.93–4.06) | 3.91 (3.79–4.02) | 3.54 (3.36–3.72) | | | |
| In (PI) | 2.13 (2.07–2.19) | 2.43 (2.32–2.53) | 3.02 (2.86–3.18) | | | |
| In (CPI) | 0.26 (0.22–0.30) | 0.34 (0.26–0.41) | 0.29 (0.18–0.40) | | | |
| In (PI/CPR) | 1.98 (1.94–2.03) | 2.10 (2.02–2.17) | 2.46 (2.34–2.57) | | | |
| In (PI/I) | 0.77 (0.72–0.83) | 0.84 (0.74–0.93) | 1.20 (1.05–1.34) | | | |
| Model 2 | In (HOMA-β%) | 3.97 (3.90–4.04) | 3.96 (3.84–4.07) | 3.58 (3.40–3.76) | | | |
| In (PI) | 2.15 (2.09–2.21) | 2.44 (2.34–2.54) | 2.98 (2.82–3.14) | | | |
| In (CPI) | 0.26 (0.22–0.31) | 0.35 (0.28–0.43) | 0.27 (0.16–0.38) | | | |
| In (PI/CPR) | 1.99 (1.94–2.03) | 2.10 (2.02–2.18) | 2.45 (2.33–2.57) | | | |
| In (PI/I) | 0.79 (0.73–0.84) | 0.82 (0.73–0.92) | 1.16 (1.02–1.31) | | | |
| Model 3 | In (HOMA-β%) | 4.00 (3.93–4.06) | 3.88 (3.78–3.99) | 3.53 (3.38–3.69) | | | |
| In (PI) | 2.17 (2.12–2.22) | 2.38 (2.29–2.47) | 2.94 (2.80–3.08) | | | |
| In (CPI) | 0.28 (0.24–0.32) | 0.31 (0.24–0.37) | 0.24 (0.14–0.33) | | | |
| In (PI/CPR) | 1.99 (1.94–2.04) | 2.09 (2.01–2.16) | 2.44 (2.32–2.56) | | | |
| In (PI/I) | 0.78 (0.72–0.83) | 0.85 (0.75–0.94) | 1.18 (1.03–1.32) | | | |

Data are presented for participants grouped according to their glucose tolerance. Values are normalized by natural logarithmic transformation and expressed as least squares means (95% confidence interval). Analysis of covariance and Tukey’s honestly significant difference test were used to compare each parameter among the three groups. Model 1, crude; model 2, adjustment for age and sex; model 3, adjustment for age, sex and body mass index. *P < 0.05. CPI, C-peptide index; DM, diabetes; HOMA-β%, homeostasis model assessment of β-cell function; ln, natural logarithm; PI, proinsulin; PI/CPR, proinsulin-to-C-peptide ratio; NGT, normal glucose tolerance; PDM, prediabetes; PI/I, proinsulin-to-insulin ratio.

function, we did not detect any significant differences in these markers between the NGT and PDM groups. It has been reported that PI/I might be affected by hepatic insulin clearance, and that HOMA-β% could underestimate the magnitude of the β-cell defect across declining glucose tolerance status, especially for impaired glucose tolerance. CPI is mainly used as an index of endogenous insulin secretion to select the appropriate treatment for patients with type 2 diabetes. From the present results, however, it might not be useful for estimating β-cell function in individuals with NGT, PDM or early type 2 diabetes. Therefore, fasting PI was the most sensitive to reflect glucose intolerance.

One limitation of the present study was that glucose tolerance was classified based on FPG and HbA1c levels.
Data are presented for the entire group and for participants grouped according to their glycated hemoglobin (HbA1c) levels. Values are expressed as mean ± standard deviation, median (interquartile range) or the number (%) of participants in that category. One-way analysis of variance, Kruskal–Wallis test or χ²-test were used to compare each parameter among the four groups. BMI, body mass index; FPG, fasting plasma glucose.

In conclusion, the present community-based study showed that fasting PI was the strongest associated with glucose tolerance, which present with a different pathophysiology. Thus, further studies are required to examine the usefulness of fasting PI as a marker to discriminate these conditions. Another limitation is that, because of its cross-sectional design, the present study yielded no evidence on the time course of these parameters across various stages of glucose tolerance. Third, all participants in our study were Japanese, so whether our results are applicable to non-Japanese populations remains unclear. Ethnic differences in the pathophysiological mechanisms of diabetes, including the degree of obesity and the insulin secretion capacity, have been documented between Japanese and Caucasians.

Table 3 | Anthropometric and biochemical characteristics of 441 participants without diabetes

|                           | Total participants | HbA1c quartile | P-value |
|---------------------------|--------------------|----------------|---------|
|                           | n                  | 1st Quartile   | 2nd Quartile | 3rd Quartile | 4th Quartile |
| Age (years)               | 57.4 ± 12.6        | 52.2 ± 12.8    | 56.5 ± 12.5 | 59.4 ± 11.4  | 63.8 ± 9.9   | <0.001     |
| No. women (%)             | 248 (56.2)         | 78 (51.7)      | 57 (57.0)   | 52 (64.2)    | 61 (56.0)    | 0.334      |
| BMI (kg/m²)               | 23.6 ± 3.6         | 22.7 ± 3.0     | 23.9 ± 3.7  | 24.0 ± 3.8   | 24.3 ± 3.8   | 0.002      |
| Waist circumference (cm)  | 81.1 ± 10.2        | 78.5 ± 9.0     | 81.3 ± 10.8 | 82.3 ± 10.2  | 83.5 ± 10.6  | 0.001      |
| FPG (mg/dL)               | 92 (85–98)         | 87 (83–94)     | 89 (85–94)  | 95 (90–100)  | 98 (92–105)  | <0.001     |
| HbA1c (%)                 | 5.4 (5.2–5.6)      | 5.1 (4.9–5.2)  | 5.4 (5.3–5.4) | 5.5 (5.5–5.6) | 5.9 (5.7–6.0) | <0.001     |
| Insulin (µU/mL)           | 4.1 (2.8–6.1)      | 3.8 (2.5–5.6)  | 4.0 (3.0–5.6) | 4.2 (3.0–5.9) | 5.2 (2.9–7.3) | 0.012      |
| C-peptide (ng/mL)         | 1.1 (0.9–1.6)      | 1.0 (0.9–1.4)  | 1.1 (0.9–1.6) | 1.1 (1.0–1.6) | 1.4 (1.0–1.9) | 0.002      |

Table 4 | β-Cell function evaluated by five estimation methods

|                           | HbA1c quartile |
|---------------------------|----------------|
|                           | 1st Quartile   | 2nd Quartile   | 3rd Quartile   | 4th Quartile   |
| Model 1                   |                |                |                |                |
| ln(HOMA-β%)               | 4.00 (3.91–4.10) | 4.06 (3.94–4.17) | 3.93 (3.80–4.06) | 3.89 (3.78–4.00) |
| ln(PI)                    | 2.05 (1.97–2.14) | 2.19 (2.08–2.29) | 2.25 (2.13–2.36)* | 2.41 (2.31–2.51)** |
| ln(CPI)                   | 0.24 (0.18–0.30) | 0.30 (0.22–0.37) | 0.28 (0.19–0.36) | 0.32 (0.25–0.39) |
| ln(PI/CPR)                | 1.95 (1.88–2.01) | 2.00 (1.92–2.07) | 2.03 (1.94–2.11) | 2.10 (2.03–2.18)* |
| ln(PI/I)                  | 0.76 (0.68–0.84) | 0.76 (0.66–0.86) | 0.77 (0.66–0.88) | 0.86 (0.76–0.95) |
| Model 2                   |                |                |                |                |
| ln(HOMA-β%)               | 3.96 (3.86–4.06) | 4.05 (3.93–4.17) | 3.95 (3.81–4.08) | 3.94 (3.83–4.06) |
| ln(PI)                    | 2.06 (1.98–2.15) | 2.20 (2.10–2.31) | 2.28 (2.17–2.39)* | 2.42 (2.32–2.52)** |
| ln(CPI)                   | 0.23 (0.17–0.29) | 0.31 (0.23–0.38) | 0.30 (0.22–0.38) | 0.35 (0.27–0.42) |
| ln(PI/CPR)                | 1.96 (1.89–2.02) | 2.00 (1.93–2.08) | 2.03 (1.94–2.11) | 2.09 (2.02–2.17)* |
| ln(PI/I)                  | 0.79 (0.71–0.88) | 0.77 (0.67–0.87) | 0.77 (0.66–0.88) | 0.83 (0.73–0.93) |
| Model 3                   |                |                |                |                |
| ln(HOMA-β%)               | 4.04 (3.95–4.13) | 4.02 (3.91–4.12) | 3.89 (3.78–4.01) | 3.87 (3.77–3.97) |
| ln(PI)                    | 2.13 (2.05–2.20) | 2.18 (2.09–2.27) | 2.24 (2.14–2.34) | 2.36 (2.27–2.45)** |
| ln(CPI)                   | 0.28 (0.23–0.33) | 0.29 (0.22–0.35) | 0.27 (0.20–0.34) | 0.30 (0.24–0.36) |
| ln(PI/CPR)                | 1.97 (1.90–2.03) | 2.00 (1.92–2.08) | 2.02 (1.94–2.11) | 2.09 (2.01–2.16) |
| ln(PI/I)                  | 0.76 (0.68–0.84) | 0.78 (0.69–0.88) | 0.79 (0.68–0.90) | 0.86 (0.76–0.95) |

Data are presented for participants grouped by glycated hemoglobin (HbA1c) level. Values are normalized by natural logarithmic transformation and expressed as least squares means (95% confidence interval). Analysis of covariance and Tukey’s honestly significant difference test were used to compare each parameter among the four HbA1c quartiles. Model 1, crude; model 2, adjustment for age and sex; model 3, adjustment for age, sex and body mass index. *P < 0.05 versus 1st Quartile, and **P < 0.05 versus 2nd Quartile. CPI, C-peptide index; HOMA-β%, homeostasis model assessment of β-cell function; ln, natural logarithm; PI, proinsulin; PI/CPR, proinsulin-to-C-peptide ratio; PI/I, proinsulin-to-insulin ratio.

Prediabetes includes impaired fasting glucose and impaired glucose tolerance, which present with a different pathophysiology. Thus, further studies are required to examine the usefulness of fasting PI as a marker to discriminate these conditions. Another limitation is that, because of its cross-sectional design, the present study yielded no evidence on the time course of these parameters across various stages of glucose tolerance. Third, all participants in our study were Japanese, so whether our results are applicable to non-Japanese populations remains unclear. Ethnic differences in the pathophysiological mechanisms of diabetes, including the degree of obesity and the insulin secretion capacity, have been documented between Japanese and Caucasians.
Considering that fasting PI levels were increased in participants with PDM, fasting PI is the most sensitive to reflect glucose intolerance.

ACKNOWLEDGMENTS
We express special gratitude to all the participants from Suttu, Hokkaido, Japan. This work was supported by Integration Research for Agriculture and Interdisciplinary Fields (No. 14538261) and the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number JP26670322. We thank Louise Adam, ELS(D), from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

DISCLOSURE
The authors declare no conflict of interest.

REFERENCES
1. U.K. Prospective Diabetes Study Group. U.K. prospective diabetes study 16. Overview of 6 years’ therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes 1995; 44: 1249–1258.
2. Butler AE, Janson J, Bonner-Weir S, et al. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 2003; 52: 102–110.
3. Rhodes CJ. Type 2 diabetes—a matter of beta-cell life and death? Science 2005; 307: 380–384.
4. Kendall DM, Cuddihy RM, Bergenstal RM. Clinical application of incretin-based therapy: therapeutic potential, patient selection and clinical use. Am J Med 2009; 122: S37–S50.
5. Yagihashi S, Inaba W, Mizukami H. Dynamic pathology of islet endocrine cells in type 2 diabetes: β-Cell growth, death, regeneration and their clinical implications. J Diabetes Investig 2016; 7: 155–165.
6. Salunkhe VA, Veluthakal R, Kahn SE. Novel approaches to restore beta cell function in prediabetes and type 2 diabetes. Diabetologia 2018; 61: 1895–1901.
7. Nakamura A, Miyoshi H, Ukawa S, et al. Serum adiponectin and insulin secretion: a direct or inverse association? J Diabetes Investig 2018; 9: 1106–1109.
8. The Committee of Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. J Diabetes Investig 2010; 1: 212–228.
9. Heianza Y, Hara S, Arase Y, et al. Hba1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. Lancet 2011; 378: 147–155.
10. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–419.
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 investig 2011; 2: 297–303.
12. Loopstra-Masters RC, Haffner SM, Lorenzo C, et al. Proinsulin-to-C-peptide ratio versus proinsulin-to-insulin ratio in the prediction of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS). Diabetologia 2011; 54: 3047–3054.
13. Breuer TG, Menge BA, Banasch M, et al. Proinsulin levels in patients with pancreatic diabetes are associated with functional changes in insulin secretion rather than pancreatic beta-cell area. Eur J Endocrinol 2010; 163: 551–558.
14. Yoshioka N, Kuzuya T, Matsuda A, et al. Serum proinsulin levels at fasting and after oral glucose load in patients with type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1988; 31: 355–360.
15. Vangipurapu J, Stančáková A, Kuulasmaa T, et al. Both fasting and glucose-stimulated proinsulin levels predict hyperglycemia and incident type 2 diabetes: a population-based study of 9,396 Finnish men. PLoS ONE 2015; 10: e0124028.
16. Kahn SE, Carr DB, Faubienbach MV, et al. An examination of beta-cell function measures and their potential use for estimating beta-cell mass. Diabetes Obes Metab 2008; 10 (Suppl. 4): 63–76.
17. Festa A, Williams K, Hanley AJ, et al. Beta-cell dysfunction in subjects with impaired glucose tolerance and early type 2 diabetes: comparison of surrogate markers with first-phase insulin secretion from an intravenous glucose tolerance test. Diabetes 2008; 57: 1638–1644.
18. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006; 29: 1130–1139.
19. Möller JB, Dalla Man C, Overgaard RV, et al. Ethnic differences in insulin sensitivity, beta-cell function, and hepatic extraction between Japanese and Caucasians: a minimal model analysis. J Clin Endocrinol Metab 2014; 99: 4273–4280.
20. Möller JB, Pedersen M, Tanaka H, et al. Body composition is the main determinant for the difference in type 2 diabetes pathophysiology between Japanese and Caucasians. Diabetes Care 2014; 37: 796–804.