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ORIGINAL ARTICLE

Relationship and factors responsible for regulating fasting and post-challenge plasma glucose levels in the early stage development of type 2 diabetes mellitus

Sae Aoyama-Sasabe[1], Xin Xin[2], Ataru Taniguchi[3], Yoshikatsu Nakai[4], Rie Mitsui[5], Hideaki Tsuji[6], Daisuke Yabe[7], Koichiro Yasuda[8], Takeshi Kurose[7], Nobuya Inagaki[9], Yutaka Seino[7], Mitsuo Fukushima[1]*

[1]Division of Clinical Nutrition and Internal Medicine, Department of Nutritional Science, Faculty of Health and Welfare Science, [2]Department of Systems Engineering, Faculty of Computer Science and Systems Engineering, [6]Department of Nutritional Science, Faculty of Health and Welfare Science, Okayama Prefectural University, Okayama, [3]Division of Diabetes and Endocrinology, Kyoto Preventive Medical Center, [4]Kyoto Institute of Health Science, [9]Department of Diabetes and Clinical Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, [5]Center for Preventive Medicine, St. Luke's International Hospital, Tokyo, [7]Division of Diabetes, Clinical Nutrition and Endocrinology, Kansai Electric Power Hospital, and [8]Department of Diabetes and Endocrinology, Saiseikai Noe Hospital, Osaka, Japan

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***Correspondence**
Mitsuo Fukushima
Tel.: +81-866-94-2151
Fax: +81-866-94-2151
E-mail address: fukushima7788@yahoo.co.jp

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ABSTRACT

Aims/Introduction: Elevation of 2-h plasma glucose (2-h PG) levels keeps step with fasting plasma glucose (FPG) levels elevation, but some individuals show dominant elevation of 2-h PG and others FPG. We analyzed dependent and independent relationships between 2-h PG and FPG, and investigated the factors regulating 2-h PG and FPG.

Materials and Methods: In 1,657 Japanese participants who underwent a 75-g oral glucose tolerance test at the initial examination for a medical check-up, we carried out simple linear regression analysis between 2-h PG and FPG levels on the three patterns of independent variables. We divided the participants into two subgroups: the 2-h PG-side group and the FPG-side from the regression line, and examined the relationships between 2-h PG-FPG and factors responsible for elevation of plasma glucose levels.

Results: There was a significant positive correlation between 2-h PG and FPG levels. The regression line of both 2-h PG and FPG as independent variables was in accordance with the regression line of 2-h PG as an independent variable and FPG as a dependent variable. In 2-h PG-side group, age was the independent factor affecting 2-h PG in addition to insulinogenic index and insulin sensitivity index (ISI composite). In the FPG-side group, triglyceride was the independent factor affecting FPG in addition to insulinogenic index and ISI composite.

Conclusions: Two-hour PG was an independent predictor of FPG. In addition to the importance of decreased insulin secretion and insulin sensitivity, age was the strong factor to elevate 2-h PG levels in the 2-h PG-side group and triglyceride was the strong factor to elevate FPG levels in the FPG-side group in the early stage of development of type 2 diabetes.

INTRODUCTION

Diagnosis of diabetes is based on 2-h plasma glucose (2-h PG) and fasting plasma glucose (FPG) levels during a 75-g oral glucose tolerance test (OGTT). Elevation of 2-h PG levels keeps step with FPG levels elevation; however, individuals showing dominant elevation of 2-h PG levels and showing dominant elevation of FPG levels exist. In addition, subjects with borderline hyperglycemia are categorized as impaired glucose tolerance (IGT), and subjects with impaired fasting glucose (IFG) are reported to have different pathophysiologies and phenotypes[1,2]. As IGT and IFG are reported to have a different

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incidence of the development of diabetes and microvascular complications[3–6], hyperglycemic status in view of 2-h PG and FPG levels shows a wide variety of pathophysiology, development of diabetes and complications.

Type 2 diabetes consists of two main factors: decreased insulin secretion and insulin sensitivity. There is a significant linear relationship between 2-h PG and FPG levels, but there is also a mechanism to regulate differently. It is still controversial as to which factor is responsible for the elevation of 2-h PG and FPG levels. Some researchers described various factors, such as insulin secretory capacity, insulin resistance, age, body mass index (BMI), triglycerides and ethnicity, that influenced the elevation of 2-h PG levels[1,2,7–13]. In contrast, insulin resistance, decreased insulin secretory capacity, BMI, ethnicity and triglycerides were reported as factors influencing the elevation of FPG levels[2,7–10,13,14].

Elevation of 2-h PG levels is an important factor, having a significant impact on cardiovascular disease (CVD) risk of patients with type 2 diabetes and borderline hyperglycemia. Large population studies, such as DECODE, Funagata and the DECODA study[3–5], reported that post-challenge blood glucose levels are recognized to be crucial because IGT patients have a higher risk of CVD and mortality than IFG patients. Recently, Ning *et al.*[6] reported that elevated 2-h PG level is associated with increased CVD mortality within the normoglycemic range in Europeans. Therefore, investigation of the factors elevating 2-h PG levels will be helpful to understand the pathophysiology and preventive strategies of diabetes and cardiovascular complications.

In the present study, we analyzed the relationship of 2-h PG and FPG levels using mathematical analysis. We investigated the dependent and independent relationships between 2-h PG and FPG levels from the OGTT examinations, and the mechanism regulating 2-h PG and FPG levels. We analyzed the factors responsible for elevation of 2-h PG and FPG levels dividing participants into two subgroups: dominant elevation of 2-h PG levels and dominant elevation of FPG levels.

METHODS

Participants

We obtained clinical data from 1,657 participants who underwent 75-g OGTT owing to a positive urine glucose test; >5.5% glycated hemoglobin (HbA1c) level; family history of diabetes at initial examination for medical check-up at Kyoto University Hospital, Ikeda Hospital, Kansai Electric Power Hospital, Kansai Health Management Center, Center for Preventive Medicine of St. Luke's International Hospital and Kyoto Preventive Medical Center from 1993 to 2011. We excluded data from patients with hypertension, hepatic or renal dysfunction, endocrine or malignant disease, and a history of heavy exercise, gastrostomy or medication, which are known to affect glucose metabolism. Originally, 358 patients who had hypertension; hepatic, pancreatic or renal dysfunction; endocrine or malignant disease; or a history of heavy exercise, gastrectomy or medication known to affect glucose metabolism were excluded from the 2,193 patients. Among 1,853 patients, 196 patients were excluded because of FPG levels <60 mg/dL and >140 mg/dL or 2-h PG levels <60 mg/dL and >250 mg/dL for the present study to analyze the factors involved in the early stage of development of type 2 diabetes, and 1,657 patients were included. The study was designed in compliance with the ethics regulations of the Helsinki Declaration, and the study protocol was approved by the ethics committee of Okayama Prefectural University.

For measurement of plasma glucose and serum insulin during OGTT, we obtained fasting, 0.5-h, 1-h, 1.5-h and 2-h blood samples after oral administration of 75-g glucose. Standard OGTT with 75-g glucose was administered according to the National Diabetes Data Group recommendations, which requires subjects to fast overnight for 10–16 h before blood collection[15]. We measured HbA1c, triglyceride (TG), total cholesterol and high-density cholesterol (HDL-cholesterol) levels at fasting samples.

Laboratory Procedures

We measured plasma glucose and serum insulin levels in the blood samples during OGTT. Plasma glucose level was determined by the glucose oxidase method using a Hitachi Automatic Clinical Analyzer 7170 (Hitachi Co. Ltd., Tokyo, Japan). Serum insulin level was measured by chemiluminescent immunoassay (ARCHITECT insulin assay; Abbot Laboratories, Abbot Park, IL, USA). Serum total cholesterol and TG levels were measured as reported previously[16]. HbA1c was measured by HLC-723G7 (Tosoh Corp., Tokyo, Japan); and the HbA1c value, estimated as a National Glycohemoglobin Standardization Program equivalent value, was calculated by the formula: HbA1c (Japan Diabetes Society) +0.4% following the previous Japanese standard measurement methods[17]. Early insulin secretion was calculated using the formula for insulinogenic index: ($insulin_{0.5}$ – $insulin_0$ [pmol/L]) / ($glucose_{0.5}$ – $glucose_0$ [mmol/L])[18]. Insulin sensitivity was evaluated by insulin sensitivity index (ISI) composite: 10,000 / ([$glucose_0$ × $insulin_0$] × [mean $glucose_{0–2}$ × mean $insulin_{0–2}$])[19]. Disposition index (DI) was expressed as the multiplex of the indices of insulin secretion and insulin sensitivity[20].

Analytical Procedures and Statistical Analyses

We carried out simple linear regression analysis between 2-h PG levels on the *x*-axis and FPG levels on the *y*-axis. We drew a straight regression line based on the least squares method according to the three patterns of independent variables:

Analysis A: Minimize the distance parallel to the *y*-axis; 2-h PG levels as an independent variable and FPG levels as a dependent variable.

Analysis B: Minimize the distance parallel to the *x*-axis; 2-h PG levels as a dependent variable and FPG levels as an independent variable.

Analysis C: Minimize the vertical distance from the regression line; both 2-h PG and FPG levels as independent variables, which was drawn by the MATLAB system (Math Works, Natick, MA, USA).

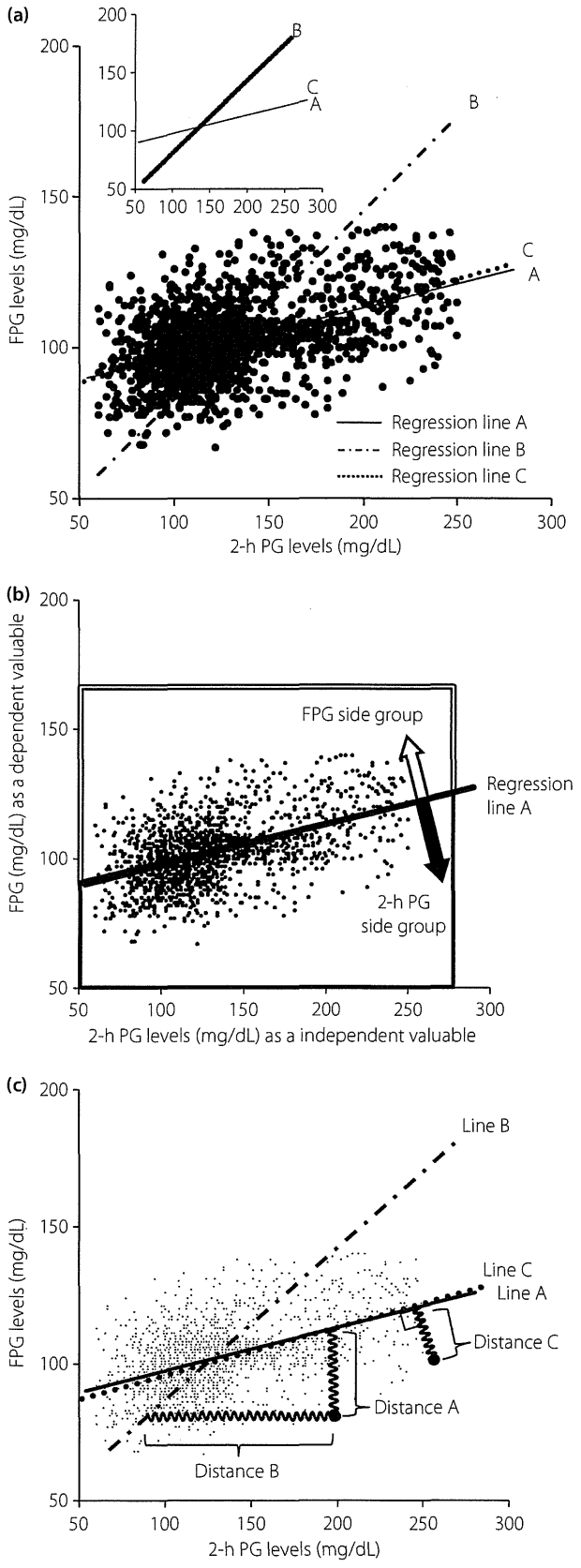

Figure 1 | (a) Simple linear regression analysis between 2-h plasma glucose (PG) and fasting plasma glucose (FPG) levels. The solid line (regression line A) indicates a regression line of 2-h PG levels as an independent variable, obtained by the least squares method minimizing the residual sum of squares; sum of distances from the regression line in parallel with the *y*-axis ($y = 0.16x + 81.70$). The dashed-dotted line (regression line B) indicates a regression line of FPG levels as an independent variable, obtained by the least squares method minimizing the sum of distances from the regression line in parallel with the *x*-axis ($y = 0.62x + 20.80$). The dotted line (regression line C) indicates a regression line of both 2-h PG and FPG levels as independent variables, obtained by the least squares method minimizing the sum of vertical distances from the regression line ($y = 0.17x + 80.11$). (b) Grouping of participants according to regression line A. The plots located below regression line A belong to the FPG side group, and the plots located above regression line A belong to the 2-h PG side group. According to the position of the plot, the plot located above the regression line belongs to the FPG side group shown by the large open arrow surrounded by a double line; in contrast, the plot located below the regression line belongs to the 2-h PG side group shown by the large closed arrow surrounded by a heavy line. (c) The view illustrates a frame format to show the method for regression line A, line B and line C. Setting the regression line by the least squares method means that the attracting force proportional to the distance from the each plots represents the strength (drawing power) of the spring. Distance A means the distance from regression line A in parallel with the *y*-axis, distance B means from regression line B in parallel with the *x*-axis and distance C means the vertical and shortest distance from regression line C.

As shown in Figure 1a, the regression line A corresponds to analysis A, the regression line B corresponds to analysis B and the regression line C minimizes corresponds to Analysis C. Figure 1b is a frame format illustrating the method for regression line A, line B and line C. Setting the regression line by the least squares method means that the attracting force in proportion to the distance from each plot represents the strength (drawing power) of the spring. Distance A means the distance from the regression line A in parallel with the *y*-axis, distance B means from the regression line B in parallel with the *x*-axis, and distance C means the vertical and shortest distance from the regression line C.

We divided the participants into two groups by the linear regression line A; locating above (*y*-axis side) or below (*x*-axis side) the regression line, with 2-h PG levels as an independent variable in the analysis A. According to the position of the plot, the plot located above the regression line belongs to the FPG side group shown by the large open arrow surrounded by a double line; in contrast, the plot located below the regression line belongs to the 2-h PG side group shown by the large closed arrow surrounded by a heavy line as shown in Figure 1c. We defined the FPG-side group as deviated to the *y*-axis, namely, the FPG-side; and the 2-h PG-side group as deviated to the *x*-axis, namely, the 2-h PG-side. To examine the clinical characteristics of the 2-h PG-side and FPG-side groups, we carried out

an unpaired Student's *t*-test between the two groups. Simple linear regression analysis was carried out for all participants to investigate the associations between 2-h PG/FPG levels and the other clinical factors, such as age, BMI, plasma glucose level, serum insulin level, HbA1c, TG, total cholesterol, HDL-cholesterol, insulinogenic index and ISI composite. $P < 0.05$ was considered as statistically significant. We carried out multivariate regression analysis to estimate the factors responsible for elevation of 2-h PG and FPG levels. All other statistical analyses were carried out using SPSS version 14.0 (SPSS, Chicago, IL, USA). All data are shown presented as mean ± standard error.

RESULTS

Clinical Characteristics of Participants

The number of participants was 1,657 in total; 954 had normal glucose tolerance (NGT), 525 had impaired glucose regulation (IGR) and 78 had diabetes mellitus (DM), according to World Health Organization criteria. The mean age of the participants was 52.8 ± 0.3 years, and BMI was 23.2 ± 0.1 kg/m^2. Parameters for glucose metabolism for the mean FPG, 2-h PG levels and HbA1c were 102.4 ± 0.3 mg/dL, 131.0 ± 1.0 mg/dL, and 5.7 ± 0.02%, respectively.

Simple Linear Regression Analysis Between 2-hPG and FPG

Figure 1a shows the simple linear regression analysis between 2-h PG (x-axis) and FPG (y-axis) levels. The series of formulas of the simple linear regression analysis are as follows: (a) analysis A: 2-h PG levels as an independent variable and FPG levels as a dependent variable; (ii) analysis B: 2-h PG levels as a dependent variable and FPG levels as an independent variable; and (iii) analysis C: both 2-h PG and FPG levels as independent variables.

Regression line A: $y = 0.16x + 81.70$

Regression line B: $x = 1.61y - 33.39$ ($y = 0.62x + 20.80$)

Regression line C: $0 = 0.17x - 0.99y + 78.97$ ($y = 0.17x + 80.11$)

There were positive correlations between 2-h PG and FPG (A: $r = 0.504$, $P < 0.0001$, B: $r = 0.504$, $P < 0.0001$). The residual sum of squares was A: 1.195×10^5, B: 1.198×10^6, respectively.

Clinical Characteristics of participant Groups With 2-h PG-Side and FPG-Side Groups

Clinical and metabolic characteristics of 2-h PG-side ($n = 885$) and FPG-side ($n = 802$) groups from the regression line are listed in Table 1. Age (54.5 ± 0.4 years *vs* 51.2 ± 0.5 years; $P < 0.0001$), BMI (23.6 ± 0.1 kg/m^2 *vs* 22.8 ± 0.3 kg/m^2; $P < 0.0001$), HbA1c (5.8 ± 0.02% *vs* 5.5 ± 0.02%; $P < 0.0001$) were higher in the FPG-side group than that in the 2-h PG-side group.

Regression Analysis Between 2-h PG and Factors Responsible for Elevation of 2-h PG in the 2-h PG-Side Group

In the 2-h PG-side group ($n = 855$), insulinogenic index ($r = -0.348$, $P < 0.0001$; Figure 2a) and ISI composite ($r = -0.328$, $P < 0.0001$; Figure 2b) showed significant correlations with 2-h PG levels in simple linear regression analysis. Age significantly correlated with 2-h PG levels ($r = 0.329$, $P < 0.0001$; Figure 2c). According to the multivariate regression analysis, age was a strong factor to predict 2-h PG levels ($\beta = 0.211$) in addition to insulinogenic index ($\beta = -0.453$) and ISI composite ($\beta = -0.337$; Table 2).

Table 1 | Clinical characteristics of participants

	Total	FPG-side group	2-h PG-side group	*P*-value
n	1,657	802	855	–
Age (years)**	52.8 ± 0.3	54.5 ± 0.4	51.2 ± 0.5	<0.0001
BMI (kg/m^2)**	23.2 ± 0.1	23.6 ± 0.1	22.8 ± 0.1	<0.0001
FPG (mg/dL)**	102.4 ± 0.3	111.1 ± 0.4	94.2 ± 0.3	<0.0001
2-h PG (mg/dL)	131.0 ± 1.0	130.6 ± 1.4	131.4 ± 1.3	NS
Fasting insulin (μU/mL)*	5.6 ± 0.1	5.9 ± 0.1	5.3 ± 0.1	<0.001
HbA1c (%)**	5.7 ± 0.02	5.8 ± 0.02	5.5 ± 0.02	<0.0001
Triglycerides (mg/dL)	123.0 ± 3	125.2 ± 4.2	120.7 ± 4.3	NS
Total cholesterol (mg/dL)	208.2 ± 1.1	207.7 ± 1.6	208.8 ± 1.6	NS
HDL cholesterol (mg/dL)	61.2 ± 0.6	61.1 ± 0.8	61.3 ± 0.9	NS
Insulinogenic index††	0.35 ± 0.01	0.30 ± 0.01	0.39 ± 0.01	<0.0001
ISI composite††	8.26 ± 0.1	7.30 ± 0.13	9.17 ± 0.15	<0.0001
Disposition index††	2.63 ± 0.08	1.96 ± 0.08	3.26 ± 0.14	<0.0001

Data are presented as mean ± standard error. Significant differences between the 2-h plasma glucose (PG)-side and fasting plasma glucose (FPG)-side groups, tested by unpaired *t*-test are: *$P < 0.001$, **$P < 0.0001$ (2-h PG-side <FPG-side), ††$P < 0.0001$ (2-h PG-side >FPG-side). BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; ISI, insulin sensitivity index; NS, not significant.

Regression Analysis Between FPG and Factors Responsible for Elevation of FPG in FPG-Side Group

In the FPG-side group ($n = 802$), insulinogenic index ($r = -0.374$, $P < 0.0001$; Figure 2d) and ISI composite ($r = -0.236$, $P < 0.0001$; Figure 2e) significantly correlated with FPG levels in simple linear regression analysis. TG significantly correlated with FPG levels ($r = 0.206$, $P < 0.0001$; Figure 2f). According to the multivariate regression analysis, TG was a strong factor to predict FPG levels ($\beta = 0.101$) in addition to insulinogenic index ($\beta = -0.482$) and ISI composite ($\beta = -0.359$; Table 2).

DISCUSSION

This is the first study to elucidate the dependent and independent relationship between 2-h PG and FPG levels mathematically, and analyze the causative factors of elevated 2-h PG and FPG levels. The regression line of both 2-h PG and FPG levels as independent variables was in accordance with the regression

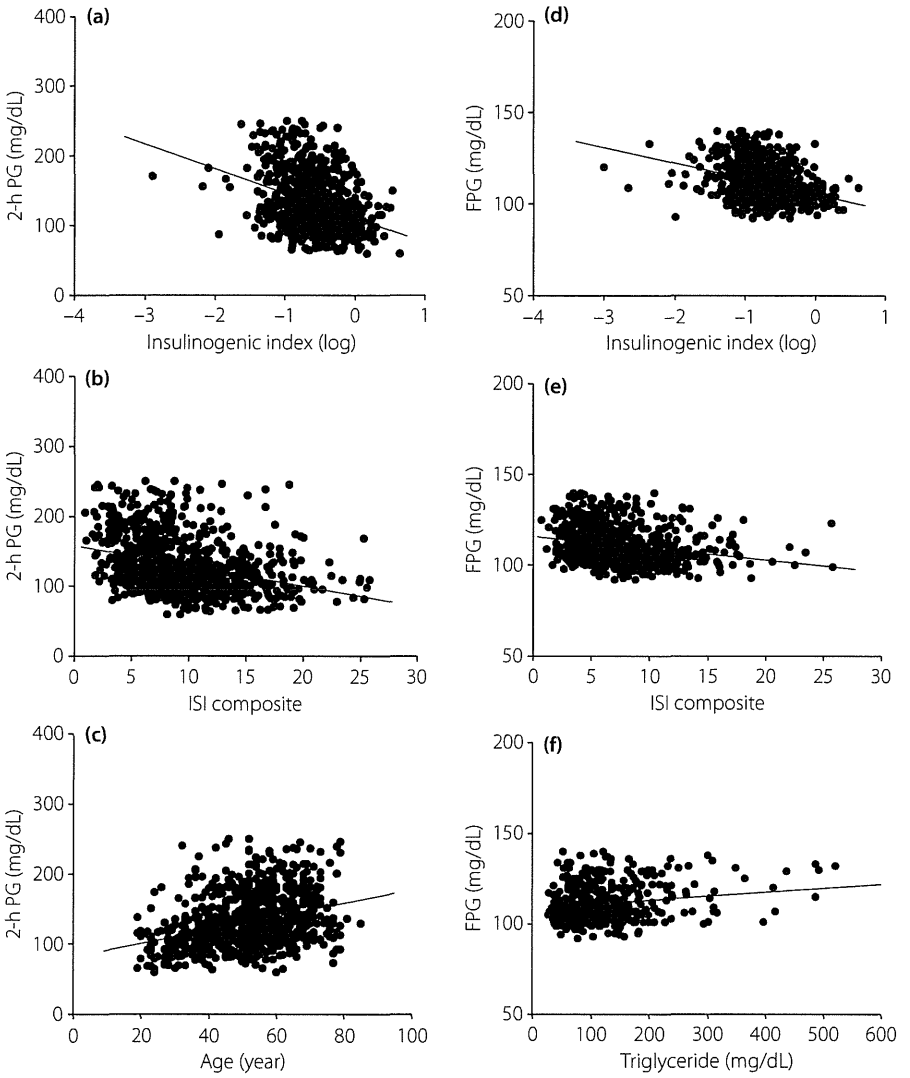

Figure 2 | (a) The relationship between insulinogenic index (log) and 2-h plasma glucose (PG) in the 2-h PG-side group ($r = -0.348$, $P < 0.0001$). (b) The relationship between insulin sensitivity index (ISI) composite and 2-h PG in the 2-h PG-side group ($r = -0.328$, $P < 0.0001$). (c) The relationship between age and 2-h PG in the 2-h PG-side group ($r = 0.329$, $P < 0.0001$). (d) The relationship between insulinogenic index (log) and FPG in the FPG-side group ($r = -0.347$, $P < 0.0001$). (e) The relationship between ISI composite and FPG in the FPG-side group ($r = -0.236$, $P < 0.0001$). (f) The relationship between triglyceride and FPG in the FPG-side group ($r = 0.206$, $P < 0.0001$).

line of 2-h PG levels as an independent variable and FPG levels as a dependent variable, showing that 2-h PG level is an independent predictor of FPG level. In the 2-h PG-side group, we showed that age was the independent strong factor for predicting 2-h PG levels in addition to insulinogenic Index and ISI composite. In the FPG-side group, we found that TG was the strong factor for predicting FPG levels in addition to insulinogenic index and ISI composite. The differences of the mechanism to elevate 2-h PG and FPG levels are shown by dividing the participants into two subgroups from the regression line; 2-h PG level is associated with age and FPG level is associated with TG.

When we set 2-h PG levels as an independent variable and FPG levels as a dependent variable, the regression line followed the linear shape in the scatter plot. In contrast, when we set FPG levels as an independent variable and 2-h PG levels as a dependent variable, the slope of the regression line was oblique, as shown in Figure 1, and the residual sum of squares was 10-fold as large as that of the regression line in which 2-h PG levels were independent (1.195×10^5 *vs* 1.198×10^6). The 2-h PG independent regression model fits to the scatter plot in comparison with the FPG independent regression model. When we set both 2-h PG and FPG levels as independent variables, the regression line approximated the line with 2-h PG as an

Table 2 | Relationship between 2-h plasma glucose and fasting plasma glucose and factors responsible for elevation of 2-h plasma glucose and fasting plasma glucose levels

Variable	Multivariate regression analysis 2-h PG levels as a dependent variable		
	β-coefficients	Standard errors	*P*-value
2-h PG-side group from the regression line			
Insulinogenic index (log)	−0.453	4.370	<0.0001
ISI composite	−0.337	0.423	<0.0001
Age	0.211	0.125	<0.0001
BMI	0.122	0.599	<0.05
TG	0.101	0.017	<0.05
Variable	Multivariate regression analysis FPG levels as a dependent variable		
	β-coefficients	Standard errors	*P*-value
FPG-side group from the regression line			
Insulinogenic index (log)	−0.482	1.030	<0.0001
ISI composite	−0.359	0.129	<0.0001
TG	0.101	0.004	<0.05
BMI	0.083	0.127	NS
Age	0.06	0.037	NS

BMI, body mass index; ISI, insulin sensitivity index; PG, plasma glucose; TG, triglyceride.

independent variable and FPG as a dependent variable. These results showed that the 2-h PG level is an inherent independent variable for representing an individual's ability to reduce blood glucose levels after the administration of exogenous glucose (i.e., glucose tolerance), and the FPG level is a dependent variable affected by a variety of factors in addition to glucose tolerance.

To further analyze the factors responsible for elevation of 2-h PG in the 2-h PG-side and FPG in FPG-side group, we investigated the relationships between 2-h PG/FPG and the factors responsible for elevation of plasma glucose. In the 2-h PG-side group, setting 2-h PG as a dependent variable, we found age was an important factor next to insulinogenic index and ISI composite among the factors responsible for elevation of 2-h PG in multivariate regression analysis. Thus, it is considered that age was a strong factor affecting 2-h PG in addition to insulin secretion and sensitivity in multivariate regression analysis. Qiao *et al.*[21] reported that age was more strongly associated with IGT than with IFG in normal Europeans. Szoke *et al.*[22] reported that insulin secretion decreases dependently on age linearly at a rate of 0.7% per year in NGT subjects evaluated by the hyperglycemic clamp. They also described IGT subjects showing a larger decrease in insulin secretion compared with NGT subjects[22]. Bando *et al.*[23] reported that the 2-h PG levels are strongly determined by age compared with FPG in Japanese subjects. Together with these observations, aging is associated with β-cell dysfunction and decreased insulin secretion, followed by 2-h PG elevation.

In the FPG-side group, setting FPG as a dependent variable, we found that TG was important next to insulinogenic index and ISI composite among the factors responsible for elevation of FPG in multivariate regression analysis. Thus, it is considered that TG was a strong factor for affecting FPG in addition to insulinogenic index and ISI composite. We previously reported that serum TG levels per se are associated with insulin action, and bezafibrate significantly improved TG levels, insulin resistance and blood glucose control in patients with diabetes[24–26]. It is considered that hypertriglyceridemia is associated with the elevation of FPG levels, and the reduction of serum TG levels improves insulin sensitivity and FPG elevation.

Insulinogenic index was the strong determinant responsible for 2-h PG and FPG levels in both the 2-h PG-side and FPG-side groups in the present study. It is still controversial as to whether decreased insulin secretory capacity or insulin sensitivity is the primary factor for elevating plasma glucose levels. Decreased insulin secretory capacity had a stronger effect to 2-h PG elevation in the studies of Japanese, Korean and Chinese subjects[11,12,27–30], whereas decreased insulin sensitivity had a stronger involvement in 2-h PG elevation in the studies of Pima Indian, American, Finnish and Caucasian studies[2,31–33]. As there are ethnic differences in the contribution of insulin secretory capacity and insulin sensitivity to plasma glucose elevation and glucose intolerance as documented previously, further studies are required to establish whether similar results are observed in other ethnic populations.

The reason for differences of metabolic characteristics between the 2-h PG side group and the FPG side group in the present study is not known at present. To compare the difference of pathophysiology between both groups, it is necessary to compare the groups to include showing the dominant elevation of only FPG levels (such as isolated-IFG) and showing the dominant elevation of only 2-h PG levels (such as isolated-IGT). In addition, a longitudinal study is necessary to show how each group will deteriorate to diabetes, respectively.

We have elucidated 2-h PG levels as an independent predictor of FPG levels. We found that 2-h PG is an inherent value representing the ability to reduce blood glucose levels after the administration of exogenous glucose (i.e., glucose tolerance), and FPG levels are the result of regulation by complex factors in addition to factors affecting glucose tolerance. Age was associated with elevation of 2-h PG levels in the 2-h PG-side group and TG was associated with elevation of FPG levels in the FPG-side group, in addition to decreased insulin secretion and insulin sensitivity. These observations will be helpful for the prevention and treatment in the early stage of development of type 2 diabetes under the consideration of the pathophysiology and phenotype of each individual.

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Social Orientation and Diabetes-Related Distress in Japanese and American Patients with Type 2 Diabetes

Kaori Ikeda[1], Shimpei Fujimoto[1,2], Beth Morling[3], Shiho Ayano-Takahara[1], Andrew E. Carroll[3], Shin-ichi Harashima[1], Yukiko Uchida[4], Nobuya Inagaki[1]*

1 Department of Diabetes, Endocrinology and Nutrition, Graduate School of Medicine, Kyoto University, Kyoto, Japan, **2** Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University, Nankoku-shi Kochi, Japan, **3** Department of Psychology, University of Delaware, Newark, DE, United States of America, **4** Kokoro Research Center, Kyoto University, Kyoto, Japan

Abstract

Objective: Recent evidence in cultural and social psychology suggests Eastern cultures' emphasis on harmony and connection with others and Western cultures' emphasis on self-direction and autonomy. In Eastern society, relational harmony is closely linked to people's well-being. The impact of this cultural and social orientation on diabetes-related distress was investigated.

Research Design and Methods: Japanese and American patients with type 2 diabetes were surveyed by well-established questionnaire in Japan and in the United States, respectively. The association of personal values for interdependence, perceived emotional support, and the Problem Areas in Diabetes scale (PAID) were analyzed.

Results: A positive correlation between interdependence and PAID ($r = 0.18$; $P = 0.025$) and a negative correlation between perceived emotional support and PAID ($r = -0.24$; $P = 0.004$) were observed after adjustments for other factors in Japanese data ($n = 149$), but not in American data ($r = 0.00$; $P = 0.990$, $r = 0.02$; $P = 0.917$, respectively, $n = 50$). In Japanese data, the three-factor structure of PAID (negative feelings about total life with diabetes, about living conditions with diabetes, and about treatment of diabetes) was identified, and interdependence showed significant positive correlations with the first and second factors and perceived emotional support showed significant negative correlations with all three factors of PAID.

Conclusions: These results suggest that personal values for interdependence may be linked to the level of diabetes-related distress and that the distress may be relieved by perception of emotional support, especially in an interdependent cultural context.

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* Email: inagaki@metab.kuhp.kyoto-u.ac.jp

Introduction

Successful diabetes care requires effective approaches to supporting behavior change of patients. Based on existing theories developed mainly in Western countries, a variety of behavioral and psychosocial interventions are implemented. Review of these interventions shows a philosophical foundation provided by "empowerment" of patients and a patient-centered approach enabling internal motivation to change [1]. Most theories emphasize changing patient behavior through the patient's own intention and ability [1]. The internally motivated "Losing weight is really important to me." replaces the externally motivated "My doctor wants me to lose weight." [2]. This concept is widely accepted and utilized by many certified diabetes educators [3]. However, external motivation may be more relevant in different cultural contexts.

Recent evidence in cultural and social psychology indicates that substantial cultural differences exist in a globalized world. In different cultural contexts, people exhibit different ways of thinking, feeling, and behaving. [4]. In the past two decades, a line of research using experimental methodologies has formed a theoretical framework comparing Western cultures (as exemplified by North American culture) with Eastern cultures (as exemplified by East Asian cultures) [5]. Western cultures are characterized by social orientation valuing "independence" or a model of agency that emphasizes self-direction and autonomy. In such cultures, people's internal attributes such as their own goals, desires and judgments form the predominant basis of their action [5]. This view is consistent with the existing theoretical foundation in diabetes intervention that focuses on the patients' internal motivation to health. In contrast, Eastern cultures such as China, Japan and Korea tend to place a higher value on "interdepen-

dence" or a model of agency emphasizing harmony, relatedness, and connection with others. In such cultures, people tend to act in consideration of the expectations, desires, and needs of others as the predominant basis of their action [5]. In these cultures, patients with diabetes often may focus on the potential deleterious effects of their lifestyle change on the people around them. Patients' perception of the expectations of others may have more impact on the ability to change their lifestyle in Eastern cultures than is found in Western cultures.

Indeed, results from social and cultural psychology indicate that these cultural differences lead to correspondingly divergent consequences in people's motivation and emotion. For example, North Americans are found to be more strongly motivated to maintain personal control while Japanese are found to be more strongly motivated toward relational harmony [6]. Attaining personal goals leads to enhanced well-being among European Americans while attainment of relational goals is more closely linked to enhanced well-being among Asian Americans and Japanese [7]. This emphasis on social relations is also shown in the result that East Asians' well-being is strongly predicted by social harmony, socially engaging emotions, and perceived emotional support from close others [8]. Perceived emotional support is a perception of receiving encouragement, compassion, and other forms of emotional support from the persons close to the respondent such as family members and friends. This result suggests that in an interdependent society people are more sensitive to the expectations of others. Similar results are shown in patients with diabetes. In Mexican Americans, who are characterized by a relatively higher tendency to interdependence than European Americans, social context reflected by the patients' perception that their family understands their diabetes is associated with patients' higher attention to self-care [5,9,10]. A family-centered approach in Taiwanese patients enhances patients' positive attitude toward diabetes [11].

The increasing rate of diabetes among Asians worldwide and Asian Americans calls for understanding the unique needs of diabetes care in Asian patients [12,13]. One notable qualitative study suggested that interdependence and reciprocal role responsibility additionally complicate disease management in Chinese American patients with type 2 diabetes [14]. The interdependent cultural contexts of East Asian society may be an important way to conceptualize the unique needs of Asian patients with diabetes. However, not all members of a culture internalize its values to the same degree; people within a culture vary in their relative agreement with interdependent or independent values [15]. Therefore, it is important to test for within-culture associations of individual difference in interdependence/independence values and individual variation in coping with diabetes.

Psychosocial assessment is recommended in routine care of patients with diabetes; emotional well-being is associated with positive diabetes outcomes [16]. Diabetes-related distress is a psychosocial issue known to impact health outcomes: it is independently associated with self-management behaviors and perceived burden of diabetes and also predicts future glycemic control [17,18]. Interdependent social orientation in Eastern cultures might therefore play a role in other psychosocial aspects of diabetes care. Strongly held personal values of interdependence may complicate diabetes care because changes in diet and lifestyle are magnified in such settings; patients who are interdependent may be more solicitous of their potential impact on others. On the other hand, perceptions of emotional support, encouragement and compassion from people around them may be especially effective for those in interdependent cultural contexts. Such emotional support may decrease the psychological burden of diabetes care on the patients personally.

In the current study, we explore differences in interdependence and perceived emotional support in relation to diabetes-related distress in two cultural backgrounds, Japan and the United States.

Methods

Participants

Participants were recruited from the Kyoto University hospital in Kyoto, Japan during the period of November 2009 through October 2010 and the Christiana Care Health System in Delaware, United States during the period of April 2010 through April 2012. Patients aged ≥30 years with type 2 diabetes for more than one year were eligible. Patients with depression were excluded from the following analysis.

Procedure

Kyoto University Graduate School and Faculty of Medicine, Ethics Committee and the Institutional Review Board of Christiana Care Health System approved the study protocol. Participants were recruited at the diabetes outpatient clinic of each hospital. All participants provided written informed consent prior to participation. The survey measuring diabetes-related distress, interdependence, and perceived emotional support were completed by all participants. The participants then completed the sociodemographic questions (age, sex, education level, and occupational status). Years from diagnosis, treatment, history of attending a diabetes patient education program and presence of diabetes complications (retinopathy, nephropathy, neuropathy, stroke, coronary heart disease, and foot ulcer) or other comorbidities needing treatment or self-management such as hypertension, heart disease, malignant tumor, and depression, were also measured by a self-report checklist. Recent glycemic control (HbA1c) was obtained from medical records.

Measurements

Diabetes related distress was measured using the Problem Areas in Diabetes scale (PAID), a well-validated 20-item self-report questionnaire [17]. Items are rated on a 5-point scale ranging from 0 (not a problem) to 4 (a serious problem). Summed scores are converted to a 0–100 scale by multiplying by 1.25 [19]. The PAID was translated into Japanese by Ishii et al. and the Japanese version also showed high internal consistency (Cronbach's $\alpha = 0.93$) and validity [20]. Interdependence was measured by a well-established English and Japanese version of the Self-Construal Scale [21,22]. Participants indicated how much they agreed with 10 independent statements (e.g., "I am not concerned if my ideas or behavior are different from those of other people", "I do my own thing, regardless of what others think.") and 10 interdependent statements about the self (e.g., "I am concerned about what people think of me", "I often have the feeling that my relationships with others are more important than my own accomplishment."). This scale has successfully measured independence and interdependence in many cultures including Japan and the United States. It distinguishes not only cultural variation but also individual variation in one culture. Measured scores are associated with psychopathological symptoms and neural activity in general population [23–25]. The score is the mean rating given to interdependent statements minus mean rating given to independent statements, which shows substantial internal reliability (split-half correlation = 0.53) [22]. Perceived emotional support was measured by a well-established English and Japanese language version of a 16-item scale assessing the perception of receiving

encouragement, compassion, and other forms of emotional support from close others. Participants were asked to think about close others and then to indicate the extent to which these close others provided each of 16 types of emotional support (Cronbach's $\alpha = 0.91$,.92, and.91, for Americans, Filipinos, and Japanese, respectively)[8]. Self-esteem was measured by Self-Competence scale, a well-established scale in English and Japanese [26,27]. HbA1c measured in US was expressed according to National Glycohemoglobin Standardization Program (NGSP) and HbA1c measured in Japan was expressed as NGSP equivalent value [28].

Data analysis

Participant characteristics and survey responses are presented as means and SD or sample size and percent. Distribution of variables was checked visually and by Shapiro-Wilk tests. Independent-sample t tests and Mann-Whitney U tests were used to explore group differences for normally distributed variables and for non-normally distributed variables, respectively. Fisher exact test was used for categorical data. Pearson's correlation coefficient was used to identify correlation among PAID, interdependence, perceived emotional support, self-esteem, and potential confounders such as sex, age and education level. The associations between PAID and interdependence and between PAID and perceived emotional support were assessed by two-way scatter plots and Pearson's correlation coefficient after adjusting for the identified confounders by regression model. To evaluate constructed factors of PAID that may have association with interdependence or perceived emotional support, the factor structure of PAID was analyzed in the Japanese data. In principal component analysis, an eigenvalue of>1.0 was used to identify the possible numbers of components. An exploratory factor analysis with promax rotation was performed. A loading level of> 0.40 was used for the items to be included in each component. The association between the identified factors of PAID and interdependence, perceived emotional support, self-esteem, sex, age, education level, HbA1c, years with diabetes, medications and complications were examined by multiple regression analyses. All analyses used Stata 11.0 (Stata Corporation, College Station, TX). Statistical significance was set at $P<0.05$ (2-tailed). Missing data were not imputed, with the exception of a maximum of 2 missing values of PAID, which were estimated using the mean of their remaining items [29].

Results

Eligible participants who completed the surveys were 152 in Japan and 64 in the United States. All 152 participants recruited in Japan were of Japanese ethnicity. Of these, three were excluded from analyses because of missing data, two for occupation and one for education. The longest experience living abroad reported by a Japanese patient was four years. Only about 21 participants recruited in the United States during the period of September 2011 through April 2012 were able to confirm ethnicity; fifteen (71%) were European Americans, four (19%) were African Americans, and two (10%) were Asian Indians. Two of the 64 participants in the United States were excluded because of depression. Twelve were excluded because of missing data, one for HbA1c, one for education, five for interdependence and five for self-esteem. Of the remaining 50 participants, one reported that she had lived in Puerto Rico for 36 years, two of them had lived in India for 35 and 21 years respectively, one had lived in Ireland, England and Germany for 30 years total, one in India and Canada for 25 years total, one in England for 11 years, and others had lived abroad for no more than one year. In this study, these 50 participants comprised the American patients. Finally, 149 Japanese patients and 50 American patients were included in the analyses (Table 1). No significant differences were observed between the two groups in sex, age, education level, HbA1c, treatment, or diabetes education history. Japanese patients had lower BMI and slightly fewer years with diabetes than American patients. More American patients had nephropathy and neuropathy. Japanese patients had a higher score of interdependence and PAID and a lower score of perceived emotional support and self-esteem than American patients.

In Pearson's correlation analysis, PAID had significant correlations with interdependence, perceived emotional support, self-esteem, sex and age in Japanese, and with self-esteem and age in Americans (Table 2). Interdependence had significant correlations with perceived emotional support, self-esteem, sex, age and education level in Japanese, and with self-esteem in Americans. Perceived emotional support had significant correlations with sex and age in Japanese, and with self-esteem in Americans. Based on these results, association between PAID and interdependence was assessed after adjusting for perceived emotional support, self-esteem, sex, age and education level. The association between PAID and perceived emotional support was also assessed after adjusting for interdependence, self-esteem, sex, age and education level. Adjusted interdependence showed a weak but significant positive association with PAID in Japanese ($n = 149$, $r = 0.18$, $P = 0.025$) (Fig. 1A), while it did not in Americans ($n = 50$, $r = 0.00$, $P = 0.990$) (Fig. 1B). Adjusted perceived emotional support showed a significant negative association with PAID in Japanese ($n = 149$, $r = -0.24$, $P = 0.004$) (Fig. 1C), but in Americans it had no association with PAID ($n = 50$, $r = 0.02$, $P = 0.917$) (Fig. 1D). The two-way distributional patterns of adjusted perceived emotional support and PAID were strikingly different between Japanese and Americans. The more emotional support Japanese patients perceived, the less distress they reported. On the other hand, American patients who perceived more emotional support did not as frequently report less distress. Confining the analysis to patients without missing data of PAID did not influence the results. Confining the analysis to those who had not lived abroad more than 5 years also did not influence the results [30].

In the Japanese patients, principal component analysis identified four factors of PAID with eigenvalue of 9.25, 1.36, 1.17, and 1.06. Each factor accounted for 46.3, 6.8, 5.8 and 5.3% of the variance, respectively. Assuming 2 to 4 factors, exploratory factor analysis was performed with promax rotation. In the 2 and 4 factor solutions, each factor was not homogeneous and hard to interpret. The conceptual congruency of items supported the 3 factors solution. The first factor included 8 items with loadings from 0.40 to 0.77, and could be interpreted as negative feelings about total life with diabetes (Table 3). The second consists of 8 items with loadings from 0.43 to 0.74, and could be interpreted as negative feelings about living conditions with diabetes. The third consists of 2 items with loadings of 0.75 and 0.77, and could be interpreted as negative feelings about treatment of diabetes. Cronbach's α as a measure of internal consistency for the 3 factors were 0.90, 0.84, and 0.82, respectively. The mean score of the items was calculated for each factor and used as a score of each subdimension of PAID. The score of the first subdimension, "negative feelings about total life with diabetes", was 1.5 ± 0.9 (mean$\pm$sd), and ranged 0 to 4. The second, "negative feelings about living conditions with diabetes", was 0.8 ± 0.7, and ranged 0 to 3.25. The third, "negative feelings about treatment of diabetes", was 1.2 ± 1.0, and ranged 0 to 4.

The association between the three subdimensions of PAID and interdependence and perceived emotional support was further evaluated by multiple regression analysis. As potential predictors of

Table 1. Characteristics of patients.

	Japanese	American	*P*
n	149	50	
Female	58 (39)	25 (50)	0.187
Age (years)	60.6±8.6 (36~81)	60.0±10.1 (33~82)	0.655†
Education (years)	14.0±2.9 (9~23)	14.6±2.4 (10~21)	0.094‡
Occupation			
Full-time job	66 (44)	22 (44)	1.000
Part-time job	20 (13)	1 (2)	0.030
Without job or retired	63 (42)	27 (54)	0.189
BMI (kg/m^2)	25.3±4.9 (15.1~53.0)	32.6±6.5 (21.0~51.4)*	<0.001‡
HbA1c (%)	7.6±1.2 (5.4~11.2)	7.6±1.6 (5.6~12.3)	0.285‡
HbA1c (mmol/mol)	60±13.1 (36~99)	60±17.5 (38~111)	
Years with diabetes (years)	10.1±8.4 (1~38)	12.0±7.4 (2~35)	0.030‡
Treatment			
Diet alone	21 (14)	2 (4)	0.072
OHA alone	82 (55)	25 (50)	0.623
Insulin alone	17 (11)	7 (14)	0.621
Insulin and OHA	29 (19)	16 (32)	0.079
Diabetes education history	74 (50)	27 (54)	0.627
Diabetes complication			
Retinopathy	24 (16)	3 (6)	0.094
Nephropathy	4 (3)	5 (10)	0.046
Neuropathy	14 (9)	11 (22)	0.027
Stroke	6 (4)	3 (6)	0.694
CHD	15 (10)	9 (18)	0.140
Foot ulcer	1 (1)	2 (4)	0.156
Major comorbidity			
Hypertention	20 (13)	8 (16)	0.643
Heart disease	10 (7)	5 (10)	0.535
Malignant tumor	1 (1)	3 (6)	0.050
Interdependence	− 0.06±0.84 (−2.7~2.6)	− 0.52±1.20 (−2.9~2.8)	0.001‡
PAID	29.8±18.7 (0~92.5)	24.9±23.1 (0~85)	0.030‡
Perceived emotional support	3.8±0.6 (1.9~5.0)	4.3±0.6 (3.0~5.0)	<0.001‡
Self-esteem	24.5±4.3 (14~38)	28.5±6.0 (17~40)	<0.001†

Data are n (%) or mean ± SD (range).
*$n=47$.
OHA, oral hypoglycemic agent; CHD, coronary heart disease; PAID, the Problem Areas in Diabetes scale.
P values are of group differences by independent-sample t tests for normally distributed variables†, Mann-Whitney U tests for nonnormally distributed variables‡, and Fisher exact test for categorical data.
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the identified three subdimensions, sex, age, education level, HbA1c, years with diabetes, medications and complications were considered to add to the three main predictors, which are interdependence, emotional support and self-esteem. Since age and education level were not significant predictors for all three subdimensions, they were removed from the model. "Negative feelings about total life with diabetes" was significantly associated with interdependence, perceived emotional support, self-esteem, sex, oral hypoglycemic agent, insulin and complications (Table 4). "Negative feelings about living conditions with diabetes" was significantly associated with interdependence, perceived emotional support, HbA1c and insulin. "Negative feelings about treatment of diabetes" was significantly associated with perceived emotional support and HbA1c.

Discussion

We investigated the contribution of social orientation emphasizing harmonious relations with others to diabetes-related distress in Japanese and American patients. The results indicate that a patients' tendency to interdependence may increase diabetes-related distress, and that a perception of encouragement and compassion from people around them may decrease the distress especially in Japanese patients living in an interdependently oriented society. In the current study, Japanese patients with higher personal values for interdependence reported higher levels

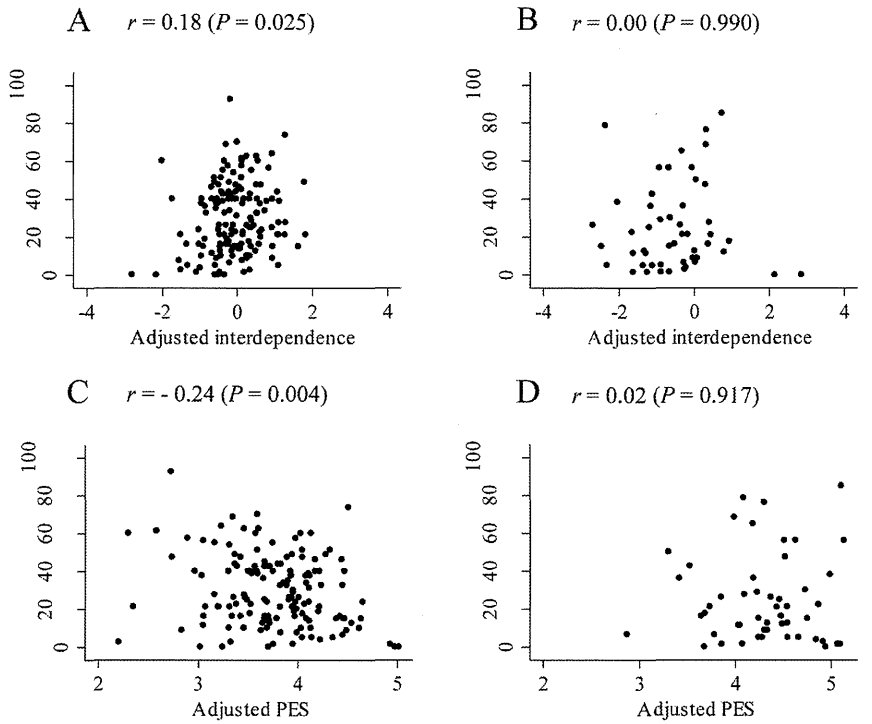

Figure 1. Distribution plots and Pearson's correlation coefficients to show the association between PAID and interdependence after adjusting for PES, self-esteem, sex, age and education level in Japanese (A) and Americans (B), between PAID and PES after adjusting for interdependence, self-esteem, sex, age and education level in Japanese (C) and Americans (D). PAID, the Problem Areas in Diabetes PES, perceived emotional support.
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of distress, and Japanese patients who perceived more emotional support reported lower levels of distress.

Such cross-sectional correlations need to be cautiously interpreted. An interdependent social orientation is reflected in one's generalized pattern of thought, feeling, and action [5,15]; among patients who value harmonious relations with the people around them, diabetes self-care requires adjustments to relationships that will add additional distress to the patients. Japanese patients who are interdependent may be especially conscious of, and concerned about, the impact of their required lifestyle changes on close others.

Notably, the association between perceived emotional support and diabetes-related distress observed in Japanese patients was not observed at all in American patients. Although the perceived emotional support addressed in the survey was general and not specific for diabetes, there was a significant negative association

Table 2. Correlations between diabetes-related distress, interdependence and perceived emotional support.

	PAID	Interdependence	PES	Self-esteem	Sex	Age
Interdependence	0.28‡	—	—	—	—	—
	0.18	—	—	—	—	—
PES	− 0.17*	0.18*	—	—	—	—
	− 0.11	− 0.03	—	—	—	—
Self-esteem	− 0.30‡	− 0.39‡	0.04	—	—	—
	− 0.39†	− 0.42†	0.38†	—	—	—
Sex	− 0.22†	− 0.22†	− 0.31‡	0.24†	—	—
	− 0.18	− 0.11	0.07	0.17	—	—
Age	− 0.16*	− 0.17*	0.17*	0.26†	− 0.06	—
	− 0.31*	− 0.07	0.00	0.04	− 0.08	—
Education	− 0.13	− 0.21†	− 0.09	0.22†	0.31‡	− 0.15
	− 0.27	0.07	− 0.12	− 0.07	0.15	0.10

Pearson's coefficients (Upper: Japanese, Lower: Americans): *$P<0.05$; †$P<0.01$; ‡$P<0.001$. PAID, the Problem Areas in Diabetes scale; PES, perceived emotional support; Sex, male = 1, female = 0.
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Table 3. Factor loadings of the 20 items of PAID for the three extracted factors after promax rotation in Japanese.

	Factor 1	Factor 2	Factor 3
Factor 1: negative feelings about total life with diabetes (α = 0.90)			
Feeling depressed when you think about living with diabetes	0.77	0.03	0.21
Feeling scared when you think about living with diabetes	0.72	− 0.20	0.43
Worrying about the future and the possibility of serious complications	0.57	0.04	0.13
Feeling angry when you think about living with diabetes	0.55	0.47	− 0.20
Feeling overwhelmed by your diabetes	0.55	0.32	0.01
Feeling constantly concerned about food and eating	0.45	0.23	0.12
Feelings of guilt or anxiety when you get off track with your diabetes management	0.40	0.35	0.01
Not "accepting" your diabetes	0.40	0.07	0.11
Factor 2: negative feelings about living conditions with diabetes (α = 0.84)			
Feeling alone with your diabetes	0.02	0.74	− 0.06
Feeling that your friends and family are not supportive of your diabetes management efforts	− 0.09	0.62	0.17
Feeling that diabetes is taking up too much of your mental and physical energy every day	0.24	0.55	0.02
Feeling "burned out" by the constant effort needed to manage diabetes	0.17	0.51	0.19
Not knowing if your mood or feelings are related to your diabetes	0.39	0.47	− 0.04
Feeling unsatisfied with your diabetes physician	− 0.18	0.47	0.20
Uncomfortable social situations related to your diabetes care (e.g., people telling you what to eat)	− 0.00	0.46	0.30
Worrying about low blood sugar reactions	0.23	0.43	− 0.20
Factor 3: negative feelings about treatment of diabetes (α = 0.82)			
Not having clear and concrete goals for your diabetes care	0.12	− 0.01	0.77
Feeling discouraged with your diabetes treatment plan	0.09	0.06	0.75
Unclassified items			
Feelings of deprivation regarding food and meals	0.19	0.39	0.13
Coping with complications of diabetes	0.30	0.12	0.38

PAID; the Problem Areas in Diabetes scale.
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Table 4. Standardized partial regression coefficients of potential predictors for the three PAID subdimensions in Japanese.

Predictor variables	Dependent variables		
	Negative feelings about total life with diabetes	Negative feelings about living conditions with diabetes	Negative feelings about treatment of diabetes
Interdependence	0.21 (0.009)	0.17 (0.047)	0.11 (0.215)
PES	− 0.19 (0.013)	− 0.21 (0.012)	− 0.23 (0.008)
Self-esteem	− 0.21 (0.008)	− 0.13 (0.121)	− 0.15 (0.091)
Sex	− 0.17 (0.030)	− 0.10 (0.245)	− 0.06 (0.481)
HbA1c	0.14 (0.062)	0.20 (0.012)	0.26 (0.002)
Years with diabetes	− 0.06 (0.388)	− 0.07 (0.386)	− 0.15 (0.064)
OHA	0.19 (0.012)	0.12 (0.126)	0.04 (0.598)
Insulin	0.16 (0.045)	0.19 (0.022)	0.05 (0.531)
Complications	− 0.17 (0.020)	− 0.12 (0.112)	− 0.09 (0.231)
Adjusted R^2 of overall model	0.28 (<0.001)	0.19 (<0.001)	0.15 (<0.001)

PAID, the Problem Areas in Diabetes scale; PES, perceived emotional support; Sex, male = 1, female = 0; OHA, oral hypoglycemic agent, use = 1, nonuse = 0; Insulin, use = 1, nonuse = 0; Complications, if any = 1, none = 0.
Data are standardized partial regression coefficients of each predictor with *P* values in parenthesis and adjusted R^2 of overall model with *P* values in parenthesis.
Age and education level were removed from the models because they were insignificant predictors for all three subdimensions.
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with diabetes-related distress. This suggests that patients' feelings that close others encourage and empathize with them may play an especially important role in diabetes self-care in a highly interdependent culture. This finding replicates past studies in which perceived emotional support was positively related to subjective well-being among Filipinos and Japanese, but not among Americans [8].

Japanese patients with higher interdependence were more likely to experience distress related to life with diabetes than to treatment of diabetes. This seems reasonable considering that interdependence affects total life and living conditions with diabetes but not treatment of diabetes. In addition, higher self-esteem may be effective in reducing the distress related to total life with diabetes, but the effect of self-esteem was smaller and was not related to the distress related to living conditions with diabetes and treatment of diabetes. Self-esteem measured in this study was confidence in one's ability not specific for diabetes. The result indicates that Japanese patients with high confidence in their general ability may be relatively resistant to distress related to total life with diabetes, but that their tendency to interdependence may increase the distress related to total life with diabetes.

Perceived emotional support had a general positive effect in all three subdimensions of distress. In an interdependent society such as Japan, encouragement and compassion from people around them may have a wide range of effects on diabetes-related distress. Among other potential contributors to diabetes-related distress, male sex was significantly associated with a lower level of distress about total life with diabetes, and poor control was significantly associated with higher level of distress about living conditions with diabetes and treatment with diabetes. Duration of diabetes was not a significant contributor to diabetes-related distress in this study. These results accord with a previous report [18,19,29].

Patients treated by medication had a higher level of distress related to total life and living conditions with diabetes but not to treatment. This result suggests that negative feelings about treatment do not necessarily stem from the medication itself. However, the result also suggests that medication itself may nevertheless be an important factor in increasing distress related to total life and living conditions with diabetes. We also found a counterintuitive association between diabetes complications and distress. Patients without any diabetes complications showed a higher level of distress related to total life with diabetes. One possible explanation is that patients without any complications were more anxious about developing complications than were those already having one or more complications. In this subdimension analysis, we used only Japanese data because of the small sample size of American data for factor analysis. Previously reported factor structures of PAID vary from study to study, and one to four factors are identified. Our results are relatively similar to the results in Dutch and Swedish patients [29,31].

We used well-established measures of interdependence, perceived emotional support, and diabetes-related distress and a growing body of evidence [8,17,20–22,26,27,32]. Our study found that emotional well-being of patients with diabetes was predicted by different variables in Japan than in the United States. Distress caused by diabetes self-care was influenced by both individual and cultural variation of interdependence. Cultural psychology takes the view that human cognitive and affective processes vary as a function of cultural environments that provide unique social contexts in which psychological processes develop and are shaped [4,32]. Although past research has shown that independence and interdependence are associated with a variety of daily behaviors in healthy people, the unique contribution of the present study is that it studies these cultural variables in a specific health context. Our work thus replicates and extends past work on cultural patterns to the diabetes context.

A similar comparison may be applicable to other societies and cultures; a cultural emphasis on interdependence is also known to be a characteristic of many African cultures, Latin-American cultures, and many southern European cultures [5]. Asian-American cultures within the United States are reported to similarly emphasize interdependence, although the magnitude of this difference may be smaller than in those living in Asian countries [5]. The findings in this study provide better understanding of the differences between European-American patients with diabetes and other patients. This study focuses on the difference between two cultural contexts: Japanese patients recruited in Japan and American patients recruited in the United States. It enables us to interpret the results without the influence of acculturation or linguistic barrier for minority. An important limitation of this study is the small sample size of the American patients. Further study is required to investigate the impact of individual variation of interdependence on diabetes-related distress among American patients.

This study suggests a potential link between interdependent social orientation and various outcomes of diabetes care. Interventions appropriate for interdependent social orientation are required. Family-centered approaches may be an effective option in such interdependent patients.

Supporting Information

Dataset S1
(DTA)

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Author Contributions

Conceived and designed the experiments: KI YU. Analyzed the data: KI. Wrote the paper: KI SF BM YU NI. Conducted the study: KI SF BM YU NI. Recruited subjects and collected data: KI SF BM SAT AEC SH.

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BMJ Open

Protocol for a large-scale prospective observational study with alogliptin in patients with type 2 diabetes: J-BRAND Registry

Nobuya Inagaki,[1] Kohjiro Ueki,[2] Yukio Tanizawa,[3] Hirotaka Watada,[4] Jiro Nakamura,[5] Yuichiro Yamada,[6] Iichiro Shimomura,[7] Rimei Nishimura,[8,9] Tsutomu Yamazaki,[10] Takashi Kadowaki[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Nobuya Inagaki;
inagaki@metab.kuhp.kyoto-u.ac.jp

ABSTRACT

Introduction: Dipeptidyl peptidase-4 (DPP-4) inhibitors including alogliptin are categorised as a newer class of oral hypoglycaemic, antidiabetic drugs to suppress the degradation of incretin hormones ((glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)) by DPP-4. We have scheduled a large-scale, multicentre, prospective, observational study (Japan-Based clinical ReseArch Network for Diabetes Registry: J-BRAND Registry) to construct an extensive database over a long-term clinical course in patients with type 2 diabetes receiving oral hypoglycaemic agents (OHAs) and to evaluate the safety and efficacy of alogliptin in Japanese population.

Methods and analysis: 20 000 patients with type 2 diabetes will be registered into two groups of 10 000 each: group A patients will be treated with alogliptin, while group B patients will be treated with non-DPP-4 inhibitor OHA(s). Approximately 300 institutions nationwide will enrol and assign eligible patients equally to either group. Each patient's data will be collected every 6 months for a 3-year period, during which time treatment with OHA(s) may be changed or discontinued, as per package insert for each OHA. Primary end points are safety variables to be compared between the two groups and their subgroups, with respect to hypoglycaemia, pancreatitis, skin disorders, infections and cancer. Secondary end points are efficacy variables including from-baseline changes of A1c, fasting glucose, fasting insulin and urinary albumin, which will be compared between groups/subgroups. New onset and progression of microangiopathy will also be evaluated against OHA(s). Overall, the J-BRAND Registry will evaluate the safety and efficacy of antidiabetic OHA (s) including alogliptin, based on a large-scale database.

Ethics and dissemination: This study will be conducted with the highest respect for individual participants according to this protocol, the Declaration of Helsinki, the Ethical Guidelines for Clinical Research (Japan Ministry of Health, Labour and Welfare, 2008) and relevant laws/regulations. The present study will construct a valuable database of patients with type 2 diabetes treated with OHA(s) including alogliptin.

Trial registration number: UMIN000007976.

Strengths and limitations of this study

- This study will be conducted as a first non-randomised, observational study to establish a large-scale database with regard to the safety and efficacy profiles of a dipeptidyl peptidase-4 (DPP-4) inhibitor in comparison to non-DPP-4 inhibitor oral hypoglycaemic agents.
- The database is expected to promote appropriate use of DPP-4 inhibitors when used alone or in combination with other antidiabetic agents.
- It will need several years for the full construct of database.

INTRODUCTION

Type 2 diabetes mellitus is a metabolic disease in which patients experience chronic hyperglycaemia and is very often associated with various complications including macrovascular as well as microvascular diseases, such as cardiovascular disease, retinopathy, nephropathy and neuropathy. As of 2011, an estimated 366 million people have been affected with diabetes globally including Japan, where more than 24 million people have been diagnosed or are suspected to have diabetes[1 2] and the prevalence is rapidly increasing worldwide.[1–5]

There have been different classes of agents developed for the treatment of type 2 diabetes including insulin and oral hypoglycaemic agents (OHAs).[1 3–6] Among those, incretin-related drugs have been noted in recent years as a novel class of antidiabetic agents[4–7] and are widely used in daily clinical practice, expanding the range of treatment options for patients with type 2 diabetes. Specifically, dipeptidyl peptidase-4 (DPP-4) inhibitors have attracted clinical attention because of the convenience of once-daily or twice-daily oral administration and the pancreatic β-cell protective effect,[8] which conventional OHAs for

type 2 diabetes do not usually provide. Additionally, DPP-4 inhibitors do not induce weight gain but may cause hypoglycaemia, though not frequently.[9] As a consequence, the amount of DPP-4 inhibitors prescribed has been increasing exponentially and many patients with type 2 diabetes currently receive a DPP-4 inhibitor concomitantly with other drug classes in daily clinical practice.

In order to promote appropriate use of DPP-4 inhibitors, it is necessary to investigate the safety and efficacy of combination therapies with this drug class and various other agents. For example, hypoglycaemia is one of the issues of interest, but no such data have yet been systematically obtained in association with the use of DPP-4 inhibitors. In recent reports, the possibility of an increasing risk of pancreatitis, skin disorders, infections and cancer has been suggested in DPP-4 inhibitor-treated patients[10–12]; however, these events are rare, and it seems difficult to associate the drug class with such risks on the basis of non-clinical and clinical data currently available.

A considerable number of diabetes-related databases were constructed in the USA and Europe, and their stratified analyses have provided results that associate specific drugs with efficacy or safety data.[13 14] These results have been reflected in clinical practice guidelines to establish standard treatment, making a contribution to the development of pharmacotherapy. However, there are no databases worldwide with regard to DPP-4 inhibitors, because this drug class has only recently been launched. This situation presents an urgent need to accumulate safety and efficacy data to support evidence-based medicine (EBM) for treatment with DPP-4 inhibitors and other OHAs. We therefore have scheduled a prospective, observational study (Japan-Based clinical ReseArch Network for Diabetes Registry: J-BRAND Registry) of actual cases with long-term experience in daily clinical practice: this type of research may be as useful for practising EBM as is an interventional, randomised study. Since DPP-4 inhibitors, particularly alogliptin (Nesina), have recently been implicated in a beneficial, antiatherogenic mechanism to reduce the risk of cardiovascular events,[15–17] alogliptin was chosen as a representative DPP-4 inhibitor throughout the J-BRAND Registry study. The drug will be administered to the planned 10 000 patients, as per its package insert (25 mg once daily, except for in patients associated with moderate-to-severe kidney malfunction, who are to receive either 6.25 or 12.5 mg daily at physician's discretion), while OHAs other than DPP-4 inhibitors will be used in another 10 000 patients for comparison (see Methods and analysis). Based on safety and efficacy information to be obtained through this research, we expect to construct a database of cases from daily clinical practice and hence to promote appropriate use of DPP-4 inhibitors when used alone or in combination with other agents.

METHODS AND ANALYSIS

The objective of this prospective study is to construct a database regarding the long-term (3-year) clinical course in patients with type 2 diabetes who receive OHAs in daily clinical practice and to evaluate the safety and efficacy of alogliptin, a novel DPP-4 inhibitor.

Primary end points

The incidence, type and severity of adverse events will be compared between group A patients initiated with alogliptin treatment and group B patients initiated with OHA treatment other than DPP-4 inhibitors at the time of registration (between-group comparison) and among subgroups defined by baseline characteristics and by concomitant medication (between-subgroup comparison). All adverse events will be included in the safety evaluation, and major safety concerns will include hypoglycaemia, pancreatitis, skin disorders, infections and cancer.

Secondary end points

Efficacy variables will be compared according to patient grouping or subgrouping as above. The efficacy variables will include the changes from baseline values (at the time of registration) in the levels of A1c (glycated haemoglobin (HbA1c); National Glycohemoglobin Standardization Program (NGSP)), fasting blood glucose, fasting insulin and urinary albumin, as well as the effect of OHA(s) on the new onset of microangiopathy (diabetic retinopathy, diabetic nephropathy, diabetic neuropathy) and its progression.

Other measurements

Laboratory tests include serum lipids such as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides. Standard 12-lead ECGs, weight and diastolic and systolic blood pressure in a sitting position will also be measured.

Overall study design

This is a large-scale, multicentre, prospective, observational study in which 20 000 patients with type 2 diabetes will be consecutively registered by a central registration procedure. An OHA should be newly started, added to previous treatment or switched from the previous OHA(s) in patients at the time of study registration. The type of a newly prescribed OHA will be designated hereinafter as 'start', 'addition' or 'switch'. Patients will be treated in daily clinical practice and followed up for 3 years.

A total of 20 000 patients will be registered and divided into two groups (A and B) consisting of 10 000 each, according to the type of OHA that has been started, added on or switched at the time of registration (see figure 2). Group A will include 10 000 patients treated with alogliptin, while group B will include 10 000 patients not treated with any DPP-4 inhibitor but with other OHA(s). Each participating patient will choose either treatment group according to his or her free will. Approximately 300 medical institutions nationwide will participate in the present study, and each investigational site is expected to enrol eligible patients at a 1:1 ratio as assigned to groups A and B, respectively. See Statistical

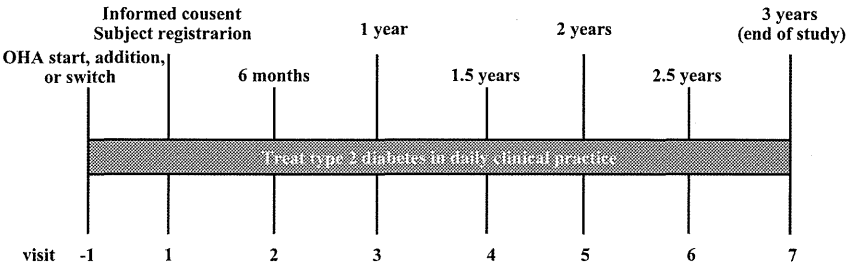

Figure 1 Schematic of study design (OHA, oral hypoglycaemic agent).

and analytical plans for the rationale for planned sample size.

The study design is schematised in figure 1.

Each participant's data will be registered every 6 months, totalling 7 times of data registration for a 3-year follow-up period (also see table 1). The 6-month interval of data registration appears reasonable to observe safety and efficacy parameters, e.g. plasma glucose control in participants who will be in daily clinical practice along with diet and exercise therapy after a change in pharmacotherapy (e.g. 'start', 'addition', 'switch' or dose increase or reduction) and to ease the burden on each participant.

Participant eligibility

Participant eligibility will be determined as summarised in box 1 (also see figure 2 for participant grouping).

Participation of a participant will be discontinued at the discretion of the principal investigator or subinvestigator if any of the following conditions occur: major protocol deviation, lost to follow-up, voluntary withdrawal, study termination, pregnancy or any other reason for which the investigator judges that discontinuation would be necessary.

Treatment

Treatment with an OHA will be provided in daily clinical practice and may be changed or discontinued within the 3-year observation period, as per the package insert for each OHA. Similarly, non-OHA antidiabetic therapies as well as treatment for concurrent medical conditions will be provided in daily clinical practice, as needed.

Study procedures

The principal investigator and subinvestigator will observe and assess each participant from the time of informed consent through the completion of observation according to the procedures depicted in table 1.

All examinations, observations and evaluations should be performed by the principal investigator (or subinvestigator) at the designated time points.

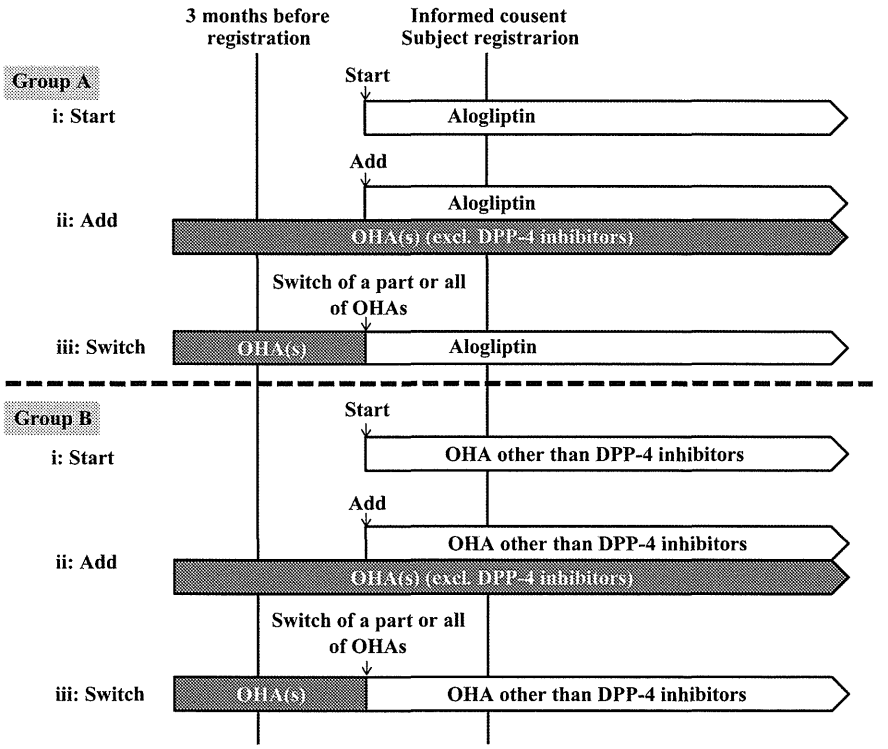

Figure 2 Schematic of participant grouping (DPP-4, dipeptidyl peptidase-4; OHA, oral hypoglycaemic agent).

Table 1 Schedule of observations

	Baseline								
	OHA start, addition or switch*	Registration	Observation period						
Study month (month)	−3	0	6	12	18	24	30	36	Early termination
Visit windows (month)	−3–0	0	1–9	10–15	16–21	22–27	28–33	34–39	–
Visit number	−1	1	2	3	4	5	6	7	–
Inclusion/exclusion criteria		X							
Informed consent		X							
Demographics		X							
Medical history/medication history (OHA)	X								
Physical examination	X	X	X	X	X	X	X	X	X
Height	X								
Waist circumference	X		(X)	X	(X)	X	(X)	X	X
Weight	X		X	X	X	X	X	X	X
Vital signs (sitting blood pressure and pulse)	X		X	X	X	X	X	X	X
Concomitant medications	←			X					X
Safety end points	X		X	X	X	X	X	X	X
Microangiopathy	X		X	X	X	X	X	X	X
Macroangiopathy	X								
Other concurrent conditions	X								
Clinical laboratory tests †	X		X	X	X	X	X	X	X
HbA1c (NGSP)	X		X	X	X	X	X	X	X
Fasting insulin†	X		(X)	X	(X)	X	(X)	X	X
Fasting blood glucose†	X		(X)	X	(X)	X	(X)	X	X
Casual blood glucose‡	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Fasting and casual C peptide	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
1,5-AG‡	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Glycoalbumin‡	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Amylase‡	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Chest X-ray‡	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
12-lead ECG ‡	(X)		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Adverse events	←			X					X

X: examination and observation must be performed.
(X): examination and observation should be performed, if required.
← X →: examination and observation must be performed throughout the period.
*The results of examination and observation of essential items and optional items performed on a day closest to the date of visit for the OHA start, addition or switch (within 6 months before registration including the day of registration) should be collected to the extent possible.
†Measurement should be performed in the fasting state (after at least 10 h of fasting), if possible.
‡Optional test items.
AG, Anhydroglucitol; HbA1c, glycated haemoglobin; NGSP, National Glycohemoglobin Standardization Program; OHA, oral hypoglycaemic agent.

Informed consent and participant registration

The principal investigator (or subinvestigator) will consecutively provide an explanation regarding the study to each eligible participant, using the informed consent document. Participants who give written consent will be registered in the electronic case report form in order, and then observations will be initiated. Participant registration will be closed at each investigational site at the time the target number of participants has been enrolled in alogliptin-treated group (group A) and DPP-4 inhibitor-untreated group (group B). The participant registration for the entire study will also be closed at the time the planned total number of participants for each group (10 000 participants) has been reached nationwide. The principal investigator will prepare a list of participant identification numbers and assign a study-specific, anonymised and uniquely given number to each participant at the time of informed consent to protect the participant's private information. These unique numbers will be used and not changed throughout the study.

Data collection

Demographics, medical history and medication history

Demographic information to be obtained will include date of birth, gender, height, weight, waist circumference,