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RESEARCH

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Sitagliptin monotherapy has better effect on insulinogenic index than glimepiride monotherapy in Japanese patients with type 2 diabetes mellitus: a 52-week, multicenter, parallel-group randomized controlled trial

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Abstract

Background: The 52-week monotherapy with the dipeptidyl peptidase-4 inhibitor sitagliptin and the sulphonylurea glimepiride on early-phase insulin secretion in Japanese patients with type 2 diabetes mellitus (T2DM) is not known.

Methods: A randomized, parallel-group, open-label trial was conducted at 18 centers between February, 2011 and March, 2013. 171 outpatients with T2DM were recruited and randomly assigned to glimepiride or sitagliptin by minimization. Doses of glimepiride (0.25–1.0 mg/day) and sitagliptin (25–100 mg/day) were adjusted for hemoglobin A1c (HbA1c) > 6.9 %. Analyses were performed on full analysis set (FAS) of randomized subjects taking medications as allocated, and underwent 75 g oral glucose tolerance test (OGTTs) before and after treatment. The primary outcome was insulinogenic index to quantify early-phase insulin secretion after treatment, which was evaluated by analysis of covariance (ANCOVA).

Results: Of 171 enrolled subjects, 68 in the sitagliptin group and 65 in the glimepiride group were included in the FAS (mean age, 64 years; baseline (HbA1c), 7.4 %). The primary outcome revealed a significantly higher insulinogenic index in the sitagliptin group than that in the glimepiride group ($p = 0.036$). Sitagliptin also reduced plasma glucose levels at 60 and 120 min during OGTT compared with glimepiride, while achieving a similar improvement in HbA1c during treatment. Body weight did not change in either of the two groups, and one case of hypoglycemia was observed in the glimepiride group.

Conclusions: Sitagliptin shows better effects on insulinogenic index after 52-week treatment compared with glimepiride in Japanese patients with T2DM.

Trial registration University hospital Medical Information Network (UMIN) Clinical Trials Registry, No.00004791.

Keywords: Clinical trial, Type 2 diabetes, Insulin secretion, DPP-4 inhibitor, Sulphonylurea

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Background

The high prevalence of type 2 diabetes mellitus (T2DM) is a worldwide public health concern. Asian countries are currently facing a greater burden of T2DM; more than 60 % of the world's T2DM patients are in Asia [1].

Efficacy evaluation of treatment with diabetes commonly uses hemoglobin A1c (HbA1c); however, the level of this index does not allow for evaluation of treatment effects on insulin secretion or insulin resistance [2–4]. β-cell function in patients with T2DM is approximately 50 % that of healthy individuals at the time of diagnosis, and decreases yearly thereafter [5]. Hence, evaluation of β-cell function as well as HbA1c is desirable for assessment of drug efficacy in treatment of diabetes. An important characteristic of T2DM is elevation of the fasting glucose level as well as that of postprandial glucose level, which are mainly affected by postprandial insulin secretion. Insulinogenic index is commonly used to assess early-phase insulin secretion in response to glucose [6–8]. It is reported that a reduced insulinogenic index represents the main abnormality in the transition from normal glucose tolerance (NGT) to T2DM, resulting in the elevation of postprandial glucose levels in Asian subjects [7–12]. In addition, maintenance of an appropriate insulinogenic index decreases incidence of microalbuminuria in T2DM [13]. Considered together, these findings suggest that the insulinogenic index may be a critical factor in progression to T2DM, maintenance of postprandial glucose levels, and prevention of the complications of diabetes.

The American Diabetes Association and European Association for the Study of Diabetes consensus for treating T2DM recommend biguanides as first-line therapy [14]. This treatment, however, has not been established in Asian countries, including Japan [15, 16]. Unlike the insulin resistance seen in Caucasians, Asian patients with T2DM have a relatively low BMI and a predominant insulin secretory defect [3, 7–12, 17–23]. Therefore, insulin secretagogues, particularly sulfonylureas and dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used in Japan [24]. Meta-analysis has shown that DPP-4 inhibitors are more effective in Asian compared to non-Asian patients [23]. Effectiveness of DPP-4 inhibitors on insulin secretion stimulated by glucose for 12-week has shown in Korean patients with T2DM [25]. However, little is known the effects of DPP-4 inhibitors on the insulinogenic index as the primary endpoint compared to sulfonylureas monotherapy.

We conducted a multicenter, randomized controlled trial to compare the effect of glimepiride and sitagliptin on the insulinogenic index after 52-week treatment in Japanese patients with T2DM.

Subjects and methods

Trial design and participants

A randomized, open-label, parallel-group trial was conducted over a period of 52 weeks from February 10, 2011 to March 31, 2013 at 18 centers across Japan, including clinics and general and university hospitals. Eligibility criteria were outpatients with T2DM aged < 80 years with an HbA1c level < 8.4 % who had received no pharmacological treatment for diabetes for at least 1 month prior to participation in this trial. Exclusion criteria were renal or liver dysfunction, pancreatic or hematological operation, severe complications of diabetes, being pregnant or possibly pregnant, malignancy under treatment and medications known to affect glucose metabolism.

Ethics

The protocol was approved by the University hospital Medical Information Network (UMIN) (Clinical Trial Registry No. 000004791), the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine, as well as the Ethics Committee of each study center. The trial was performed in accordance with the Declaration of Helsinki upon obtaining written informed consent from all participants, and was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) Statement [26].

Intervention and maintenance

Each participant was administered glimepiride (titrated upward to 1.0 mg) or sitagliptin (titrated upward to 100 mg) once daily in the morning for 52 weeks. The starting dose was decided by the respective physicians based on the baseline condition of each participant. When HbA1c levels exceeded 6.9 % after 6 months or later, glimepiride and sitagliptin doses were increased to each titrated dose. Physicians were allowed to decrease the doses at any point to prevent the occurrence of a hypoglycemic event. On the other hand, if participants did not meet the specified glycemic control criteria with the setup dose, physicians were allowed to add or switch medications and the participants were discontinued from the trial.

Outcome measurements

The primary outcome measurement was the difference in post-treatment insulinogenic index between the two groups. Secondary outcome measurements were the levels of plasma glucose (PG) (mmol/l), immunoreactive insulin (IRI) (pmol/l), C-peptide (CPR) (nmol/l), glucagon (ng/l) (Millipore Corporation, Bilerica, MA), and insulin sensitivity index (ISI; an index of insulin resistance) during 75 g oral glucose tolerance tests (OGTTs) before and after 52-week treatment [27]. In addition,

HbA1c (%), glycated albumin (GA) (%), and BMI (kg/m^2) after treatment also were evaluated as secondary outcome measurements. Each outcome was calculated as follows: HbA1c was expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the following formula: HbA1c (NGSP value) (%) = 1.02 × HbA1c (Japan Diabetes Society value) (%) + 0.25 [28]. The estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) was calculated by 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ for men, 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ × 0.739 for women [29]. The insulinogenic index was calculated by the following equation: (IRI at 30 min - fasting IRI)/(PG at 30 min—fasting PG) [6–8]. ISI composite was calculated by 10,000/{[fasting PG (mmol/l) × fasting IRI (pmol/l) × mean 75 g OGTT PG (mmol/l) × mean 75 g OGTT IRI (pmol/l)]$^{0.5}$}1/3 [27].

Sample size

Given the lack of differences and variance in the insulinogenic index between two similar groups in a previous study, an effect size of 0.6, which is conventionally accepted as a medium effect, was used to calculate an appropriate sample size. We estimated that 100 participants would provide at least 80 % power to detect a statistically significant difference ($\alpha = 0.05$, two-sided test, and withdrawal rate of 10 % per year) between the two groups.

Randomization

We used the UMIN system, a computer-generated random sequence, to assign participants to either glimepiride or sitagliptin in a 1:1 ratio by minimization, based on sex, center, age, and HbA1c. Collaborating physicians enrolled the participants, and during the follow-up period, this trial was performed without blinding. That is, both physicians and participants were aware of which drug was allocated.

Procedures

Upon obtaining informed consent, OGTTs were performed before (0 week) and after 52-week treatment. The levels of PG, IRI, CPR, and glucagon were measured at 0, 15, 30, 60, and 120 min (min) during OGTTs. After treatment, OGTTs were performed with a 24-h washout period. GA was measured at 0 and 52 weeks, and glutamic acid decarboxylase (GAD) antibody was measured at 0 week. HbA1c, PG, body weight, and clinical biochemical tests were measured (0, 4, 12, 24, 36, and 52 weeks). Safety monitoring for hypoglycemia was performed during treatment. All samples were labeled with a code assigned to each participant and routinely analyzed at a laboratory of the SRL Corporation (Tokyo, Japan).

Statistical analyses

All statistical analyses were performed with a blind procedure by an independent third party, Statcom Company Limited. For the primary outcome measurement, the main analysis was performed on the full analysis set (FAS) of all randomized participants who took medications as allocated and underwent the OGTTs before and after treatment, excluding those with a hemolyzed sample, those who were added or changed therapy, and those who were withdrawn from the trial before treatment following consent acquisition. Subgroup analysis was performed on the per-protocol set (PPS), which excluded positive result of GAD antibody, protocol violations, or poor compliance from the FAS. Analysis of covariance (ANCOVA) was used to evaluate the primary outcome measurement based on baseline log-transformed insulinogenic index, and allocation variables, including age, sex, and HbA1c as covariates. For secondary outcome measurements, repeated measures analysis using a mixed model with terms for visit, treatment, and interaction was performed for OGTT, HbA1c, and BMI, including baseline values as covariates. Least-squares means (lsmeans) with 95 % confidence intervals (CIs) were obtained from the model, estimating from the mixed model. Other secondary outcome measurements were compared between the two groups using Analysis of variance (ANOVA) for the evaluation of GA and ISI. As an exploratory analysis, the change of insulinogenic index in each group was analyzed by Paired *t* test. The achievement rate of HbA1c < 7.0 % between the two groups were compared by Fisher's Exact test. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and JMP® 9 (SAS Institute Inc., Cary, NC, USA). No interim analysis was performed.

Results

Flow chart of participants

A total of 196 participants were recruited for this trial (Fig. 1). Of these, 25 participants who did not meet the inclusion criteria were excluded. The remaining 171 participants were randomly assigned to sitagliptin or glimepiride groups in a 1:1 ratio. Of these, 133 participants (glimepiride, n = 68; sitagliptin, n = 65) were analyzed as the FAS, with a final follow-up rate of 77.8 %. In the glimepiride group, 62 participants were regarded as the PPS, which excluded six participants due to positive results of GAD antibody (n = 3), protocol violations (n = 2), or poor compliance (n = 1). In the sitagliptin group, the number of participants in the FAS and PPS was the same. The main reason for discontinuation in both groups was due to hemolysis of samples. Other reasons included dropout from treatment, addition of other

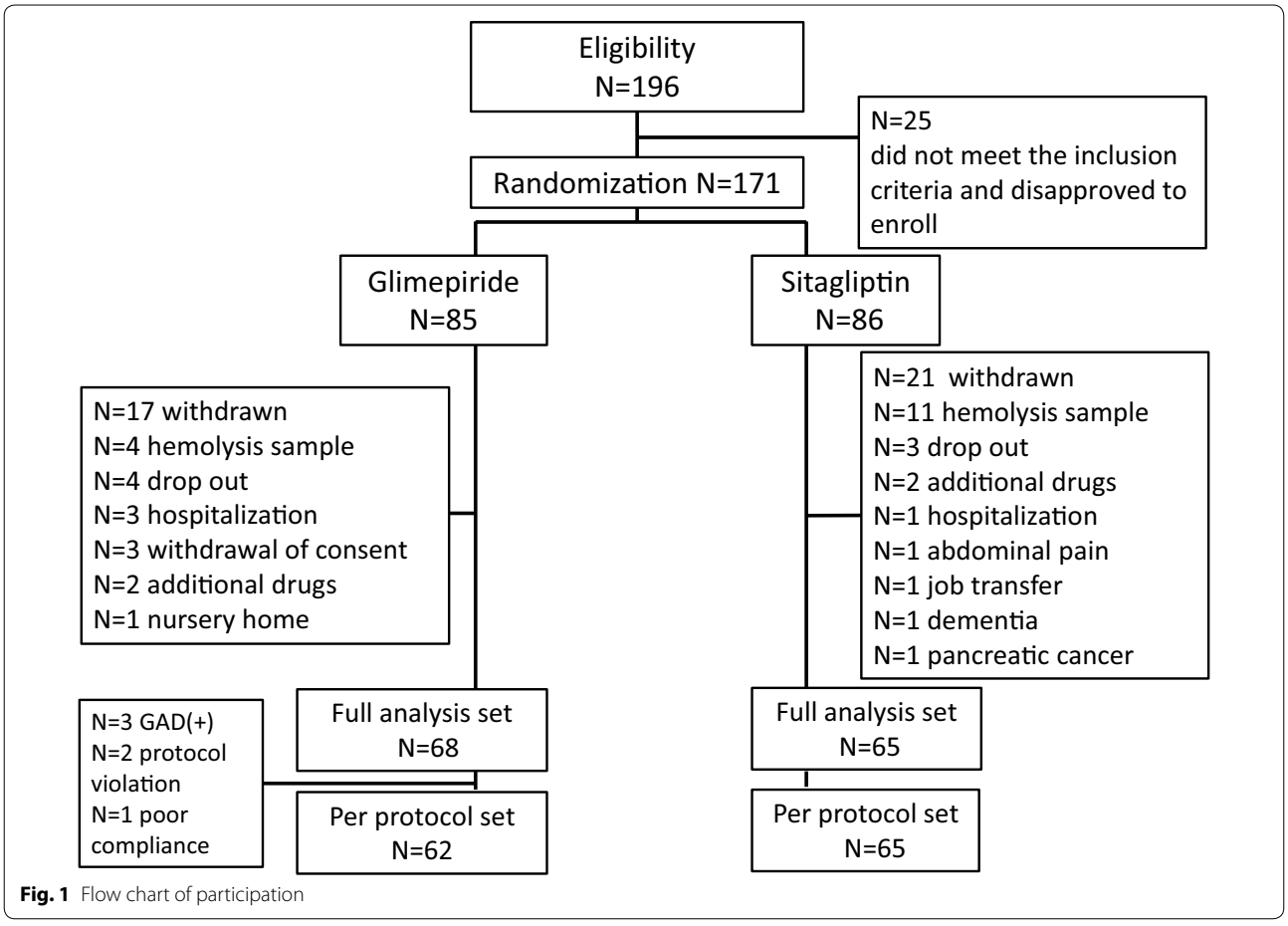

Fig. 1 Flow chart of participation

drugs due to hyperglycemia, or insulin therapy under hospitalization.

Demographics and participant characteristics in the FAS

All variables were well balanced between the two groups in FAS, and also divided into the same balance in the baseline (Table 1). Participants were middle-aged, had a mean BMI of 24.4 (3.6) (kg/m^2), had short duration of diabetes, and had no severe renal dysfunction. They had started treatment with oral hypoglycemic agents at an HbA1c of 7.4 (0.5) %. Participant characteristics (i.e., low BMI, low insulin secretion, and low insulin resistance) are comparable to those of Asian T2DM patients previously reported [3, 7–12, 17, 18, 22–25]. The usual starting dose of glimepiride was 0.5 mg/day; that of sitagliptin was 50 mg/day. Eighteen patients had taken diabetic medication before enrollment as follows; biguanide (n = 1), insulin (n = 1), glinides (n = 4), alpha glucosidase inhibitors (n = 4), and sulfonylureas (n = 8). They had not used these antidiabetic treatments for at least 3 months before enrollment. Especially, eight patients who took sulfonylureas were divided into the two groups equally.

Primary outcome measurement

Insulinogenic index after 52-week treatment was significantly higher in the sitagliptin group than in the glimepiride group ($p = 0.036$) in the FAS (Fig. 2a). No interactions between the drugs and other adjusted factors were observed. Associations between insulinogenic indices and PG levels at 60, and 120 min during OGTT were evaluated. Insulinogenic indices were more negatively correlated with PG levels at 60 min than those at 120 min ($R^2 = 16$ %, data not shown). The obtained linear regression equation in total is as follows: log post-treatment insulinogenic indices (pmol/mmol) = 4.8 − 0.1 × PG levels at 60 min (mmol/l) (R^2, coefficient of determination = 35 %, $p < 0.0001$ in total, 38 %, 30 % in sitagliptin and in glimepiride, respectively) (Fig. 1b).

Secondary outcome measurements

The levels of PG, IRI, CPR, and glucagon during OGTTs were compared after both treatments (Fig. 3). PG levels at 60 min ($p < 0.01$) and 120 min ($p < 0.001$), and overall ($p < 0.001$) were significantly lower in the sitagliptin group than those in the glimepiride group (Fig. 3a). The

Table 1 Participant characteristics in the full analysis set

Variables	Glimepiride (n = 68)	Sitagliptin (n = 65)
Male/female (number, %)	49/19 (72.1/27.9 %)	49/16 (75.4/24.6 %)
Age (year)	64 (8)	63 (9)
BMI (kg/m^2)	24.7 (3.3)	24.1 (3.8)
Duration (year)	6.0 (5.1)	6.2 (6.0)
HbA1c (NGSP, %)	7.5 (0.5)	7.4 (0.5)
GA (%)	19.5 (2.8)	19.4 (2.7)
eGFR (ml/min/1.73 m^2)	74.9 (14.0)	76.2 (17.1)
ISI (I^2/mmol pmol)	16.2 (9.2, 24.0)	16.3 (10.2, 22.0)
Log transformed insulinogenic index (pmol/mmol)	2.6 (2.1, 3.3)	2.2 (1.9, 2.8)
Starting dose (mg/day)	0.25 (20.6 %)	25 (12.3 %)
	0.5 (77.9 %)	50 (87.7 %)
	1.0 (1.5 %)	100 (0.0 %)

Data are expressed as means (SD), median with interquartile range (IQR), number (%), or percent (%)

Data were analyzed ANOVA or Fisher's Exact test

No significant differences were observed between the two groups

BMI body mass index, *HbA1c* hemoglobin A1c, *ISI* insulin sensitivity index, *GA* glycated albumin, *eGFR* estimated glomerular filtration rate

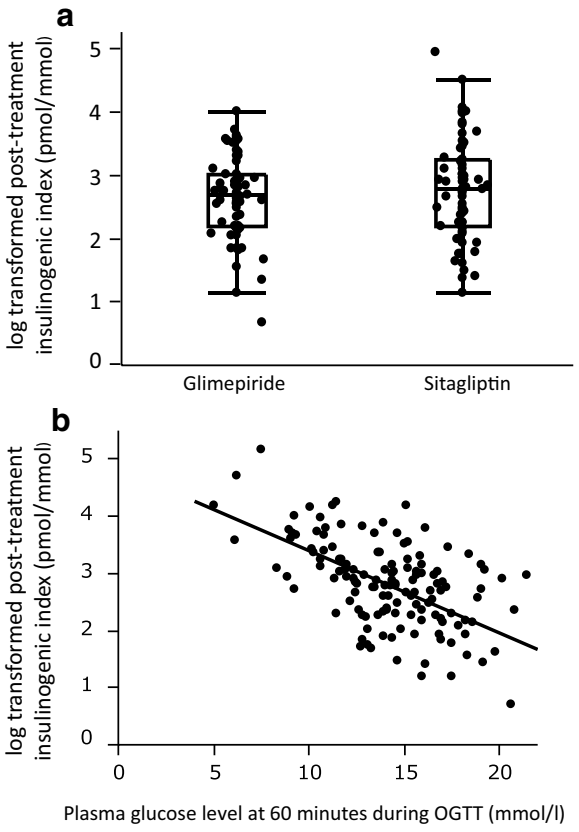

Fig. 2 **a** *Box* and *dot plots* of log-transformed post-treatment insulinogenic index for glimepiride and sitagliptin groups. Analysis of covariance (ANCOVA) revealed a significantly higher post-treatment insulinogenic index in the sitagliptin group (p = 0.036) in the FAS. **b** Scatter plot and linear regression equation in total: log post-treatment insulinogenic index (pmol/mmol) = 4.8 − 0.1 × PG at 60 min (mmol/l) (R^2, coefficient of determination = 35 %, p < 0.0001)

levels of IRI, CPR, and glucagon did not differ between the two groups (Fig. 3b–d). We also compared the levels of PG, IRI, CPR, and glucagon during OGTTs between pre-treatment and post-treatment in each group (Additional file 1: Figure S1A–H). PG levels at 30, 60, and 120 min in glimepiride group were significantly lower after treatment than those before treatment (Additional file 1: Figure S1A), while PG levels at 60 and 120 min in sitagliptin group were significantly lower after treatment than those before treatment (Additional file 1: Figure S1B). In both groups, the level of overall glucose was significantly lower than that before treatment. The overall insulin level was significantly higher after treatment only in sitagliptin group (p < 0.05) (Additional file 1: Figure S1C, D). The level of overall CPR was increased after treatment in both groups compared to that before treatment (Additional file 1: Figure S1E, F) (p = 0.001, p < 0.001, respectively). All points of insulin and C-peptide levels during OGTT did not change between before and after 52 weeks treatment in each group. The level of glucagon, including overall level, was not significantly changed between before and after treatment in each group (Additional file 1: Figure S1G, H). Insulinogenic index after treatment was significantly higher than that before treatment in each group (p < 0.05, p < 0.001, respectively) (Data not shown).

HbA1c improved gradually from 7.4 % to 6.8 (6.7–7.0) % at 12 weeks, and remained the same until 52 weeks (Additional file 2: Figure S2). There was no significant difference in HbA1c levels between the two groups during 52-week treatment. Neither the post-treatment levels of HbA1c nor GA showed significant difference in the two groups (Table 2) (p = 0.79, p = 0.3, respectively). The achievement rate of HbA1c < 7.0 % also showed no significant difference between the two groups (61.8, 67.7 %, respectively, p = 0.586). ISI was significantly and slightly higher in sitagliptin group than that in glimepride group (p = 0.046). BMI did not differ after treatment (p = 0.75) (Table 2) and during the follow-up period (data not shown) between the two groups. At 52-week, the final dose of glimepiride was 0.25 mg/day (13.2 %), 0.5 mg/day (72.1 %), and 1.0 mg/day (14.7 %), and that of sitagliptin was 25 mg/day (6.2 %), 50 mg/day (83.1 %), 75 mg/day (1.5 %), and 100 mg/day (9.2 %).

The single, self-reported episode of mild hypoglycemia was experienced during exercise in the glimepiride group; no severe hypoglycemia was reported in either group.

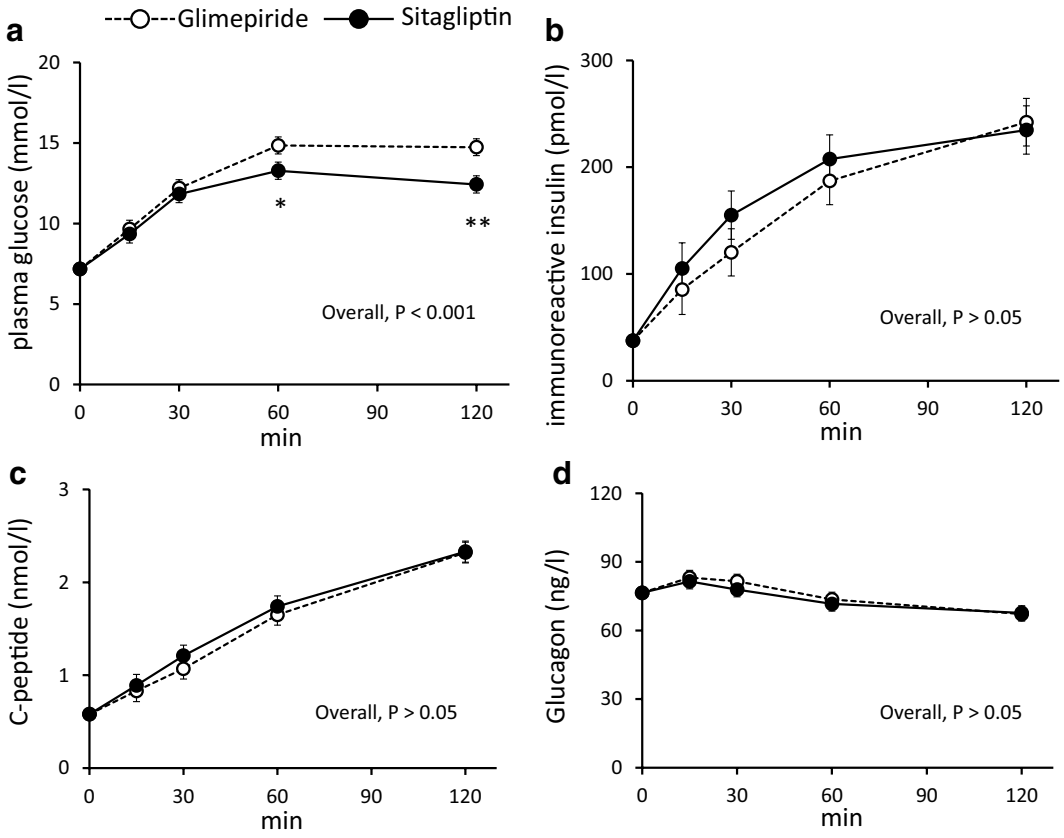

Fig. 3 The levels of PG (**a**), IRI (**b**), CPR (**c**), and glucagon (**d**) during OGTT after 52-week treatment. *Filled circles* with a *dotted line*: post-glimepiride treatment; *filled circles* with a *solid line*: post-sitagliptin treatment. Values show least-squares mean with 95 % confidence interval (CI) estimated by a mixed-model for repeated measures analysis. **a** $p < 0.001$ glimepiride vs. sitagliptin, *$p < 0.01$, ** $p < 0.001$ vs. glimepiride at each time point. **b**–**d** not significant (n.s.) at each time point

Table 2 Post-treatment comparison of physical and chemical parameters in the full analysis set

Covariates	Glimepiride (n = 68)	Sitagliptin (n = 65)	p value*
BMI (kg/m^2)	24.5 (24.2, 24.7)	24.5 (24.3, 24.8)	0.75
HbA1c (NGSP %)	6.8 (6.7, 7.0)	6.8 (6.7, 7.0)	0.79
GA (%)	17.4 (2.8)	17.7 (2.6)	0.30
ISI (I^2/mmol pmol)	15.8 (9.4, 20.8)	17.3 (11.9, 23.5)	0.046*

Data are expressed as least-squares mean with 95 % confidence interval (CI) in BMI and HbA1c, means (SD) in GA, or median with interquartile range (IQR) in ISI

Analysis of variance (ANOVA) revealed a significant difference in the two groups

BMI body mass index, *HbA1c* hemoglobin A1c, *GA* glycated albumin, *ISI* insulin sensitivity index

* Comparison of the values after 52-week treatment between glimepiride and sitagliptin groups

One participant in the sitagliptin group had abdominal pain and discontinued treatment. Three participants in the sitagliptin group showed more than a 1.3-fold increase in creatinine relative to baseline. Hepatic-related side effects were considered when laboratory values exceeded threefold upper limit of the normal range. Alanine aminotransferase (ALT) was elevated in five participants (glimepiride group, n = 1; sitagliptin group, n = 4); however, all had baseline ALT exceeding the limit of normal range. Aspartate aminotransferase (AST) was elevated in one participant in the glimepiride group.

Discussion

In this trial, sitagliptin monotherapy resulted in significantly higher insulinogenic index compared with that of glimepiride monotherapy in Japanese patients with T2DM after 52-week treatment (Fig. 2a). It is reported that the DPP-4. Inhibitors conserved β-cell function in patients with T2DM and autoimmune diabetes [30, 31]. Our result is possibly due to conserving β-cell function by DPP-4 inhibitor. In addition, the insulinogenic index was negatively correlated with glucose levels at 60 min during OGTT after treatment (Fig. 2b). This result suggests that maintenance of the insulingenic index is important to preserve postprandial glucose levels in early T2DM and

indicates that sitagliptin may have a better effect on lowering the postprandial plasma glucose levels than glimepiride in Asian patients with T2DM. It was reported that DPP-4 inhibitors including sitagliptin suppress glucagon secretion [32, 33]. However, there were no effects of sitagliptin on glucagon secretion in this trial. This result suggests that the effect of sitagliptin on insulin secretion but not on glucagon secretion might continue after a drug washout period of 24 h after 52-week treatment.

Insulin secretion stimulated by sulfonylureas is independent of the glucose concentration, while DPP-4 inhibitors increase an active form of incretin peptide by DPP-4 inhibition and potentiate glucose-dependent insulin secretion [34–36]. Accordingly, sulfonylureas are associated with risk of hypoglycemia and weight gain; DPP-4 inhibitors are associated with lower frequency of hypoglycemia and are weight neutral [34–36]. In this trial, there was no hypoglycemia or weight gain in the sitagliptin group (Tables 1 and 2). However, it should be noted that glimepiride treatment also did not induce weight gain or incidence of severe hypoglycemia (Tables 1 and 2). This might be attributed to the low-dose of glimepiride used. Based on the Japanese claims database, 72 % of patients with single sulfonylurea treatment used 1.0 mg/day for 1 year, and 70 % of the patients treated with 1.0 mg/day of glimepiride achieved 1.0 % reduction of HbA1c [37]. Thus, the dose of glimepiride was set to 1.0 mg/day in this trial. Consequently, a similar reduction in HbA1c levels was observed during 52-week treatment and no significant differences were found in HbA1c and GA levels between the two groups (Table 2, Additional file 2: Figure S2). These results made it possible to evaluate insulin secretion under the same glucose control conditions. Accordingly, the dose selection of less than 1.0 mg/day of glimepiride, the effect of which on HbA1c reduction is comparable to that of less than 100 mg/day of sitagliptin, seemed reasonable in this trial. In addition, our results also suggest that in regard to HbA1c-lowering efficacy, a low-dose of glimepiride is similarly effective as sitagliptin without weight gain or severe hypoglycemia at the early stage of T2DM with low insulin secretion (Table 2 and Additional file 2: Figure S2). Although a similar reduction in HbA1c and GA was achieved, post-challenge plasma glucose levels were significantly lower with sitagliptin than with glimepiride (Table 2, Fig. 3a, and Additional file 2: Figure S2). This result indicates that sitagliptin has better effects on insulinogenic index after 24-h wash out period at 52-week treatment.

This trial has several limitations. First, low-dose glimepiride was used in Japanese patients with T2DM who have low BMI and insulin secretion [3, 7–9, 12, 17, 22–25]. The maximum dose of glimepiride was set at 1.0 mg/day to achieve the same improvement of HbA1c between the two groups. Although a significantly better level of insulinogenic index was shown by glimepiride treatment ($p < 0.05$, data not shown), it is unknown to what extent high-dose glimepiride improves the insulinogenic index or HbA1c in Japanese patients with T2DM. Second, meal tolerance tests (MTTs) were not performed in this trial. The primary endpoint is to evaluate early-phase insulin secretion in response to glucose. The insulinogenic index has already been established as an index of early-phase insulin secretion during OGTT [6–8]. However, the indices of the meal-stimulated insulin secretion by MMTs have not established, mainly because the total calories and contents of the meal differ among the previous studies [32, 33]. Third, the follow up rate of 78 % might be relatively low. The main reason is hemolysis of samples, which are important for the calculation of insulinogenic index. If we had planned to use multiple imputation method for missing data in the protocol, we might obtain higher follow up rate. The strength of this trial lies in its design, i.e., a multicenter, randomized, controlled trial involving clinics and a university hospital, which enhances the generalizability of our results. Furthermore, an active-controlled trial comparing the most widely used insulin secretagogues is practical for a daily clinical setting. This trial focused on the pathophysiology and treatment efficacy of T2DM in Asia. Our finding of a better effect on early-phase insulin secretion is of clinical importance for Asian patients with T2DM.

In conclusion, sitagliptin showed better effects on insulinogenic index after 52-week treatment compared to glimepiride in Japanese patients with T2DM. Further research is required to assess early-phase insulin secretion in patients treated with these drugs for longer period.

Additional files

Additional file 1: Figure S1. The levels of PG (A and B), IRI (B and D), CPR (E and F), and glucagon (G and H) during OGTT before and after 52-week treatment in glimepiride (A, C, E, and G) and sitagliptin groups (B, D, F, and H). Outlined circles with a dotted line: pre-glimepiride treatment, filled circles with a solid line: post-glimepiride treatment. Outlined squares with a dotted line: pre-sitagliptin treatment, filled squares with a solid line: post-sitagliptin treatment. Values show least-squares mean with 95 % confidence interval (CI) estimated by a mixed-model for repeated measures analysis. Asterisks indicate significant differences between pre-treatment and post-treatment at each time point († $p < 0.05$, †† $p < 0.01$, ††† $p < 0.001$). A) $p < 0.001$ pre- vs. post-glimepiride. † $p < 0.05$ at 30 and 60 min and †† $p < 0.01$ at 120 min pre- vs. post-glimepiride. B) $p < 0.001$ pre- vs. post-sitagliptin. ††† $p < 0.001$ at 60 and 120 min pre- vs. post-sitagliptin, C) not significant (n.s.) at each time point, D) $p < 0.05$ pre- vs. post-sitagliptin, E) $p = 0.001$ pre- vs. post-glimepiride, F) $p < 0.001$ pre- vs. post-sitagliptin, G) n.s. at each time point, H) n.s. at each time point.

Additional file 2: Figure S2. Time course of HbA1c from baseline to 52 weeks in the FAS. White circles with a dotted line: glimepiride group, filled black circles with a solid line: sitagliptin group. Values show least-squares mean with 95 % confidence interval (CI) estimated by a mixed-model for repeated measures analysis, including terms for baseline HbA1c visit and treatment by visit interaction. There was no significant difference between the two groups at any point.

Abbreviations
T2DM: type 2 diabetes mellitus; BMI: body mass index; DPP-4: dipeptidyl peptidase-4; HbA1c: hemoglobin A1c; PG: plasma glucose; IRI: immunoreactive insulin; CPR: C-peptide; ISI: insulin sensitivity index; OGTT: 75 g oral glucose tolerance tests; GA: glycated albumin; GAD: glutamic acid decarboxylase; FAS: full analysis set; PPS: per protocol set; ANCOVA: analysis of covariance; ANCOVA: analysis of covariance; CI: confidence intervals; SD: standard deviation; IQR: interquartile range; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Authors' contributions
Author contributions were as follows: YK designed the study, wrote the research protocol, collected and managed the research data, interpreted the data, and drafted the initial manuscript; NH designed the study, wrote the research protocol, collected and managed the research data, interpreted the data, and drafted, reviewed, and edited the manuscript; AH, SK, KY, EO, SH, HY, YF, NK, and YN designed the study and collected data; FM and MS planned and performed the statistical analysis; SH managed the research data, interpreted the data, and drafted, reviewed, and edited the manuscript; TN and NI designed the study, drafted the research protocol, managed the research data, interpreted the data, and drafted, reviewed, and edited the manuscript. Nobuya Inagaki is the guarantor of this trial. All authors read and approved the final manuscript.

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Competing interests
Nobuya Inagaki served as a medical advisor for Takeda, Taisho Pharmaceutical, GlaxoSmithKline, Mitsubishi Tanabe Pharma, lectured for Merck Sharp & Dohme (MSD), Sanofi, Novartis Pharma, Dainippon Sumitomo Pharma, Kyowa Kirin, and Mitsubishi Tanabe Pharma, and received payment for his services. Nobuya Inagaki also received a clinical commissioned/joint research grant from MSD, Eli Lilly Japan, Shiratori Pharmaceutical, Roche Diagnostics, and the Japan Diabetes Foundation, and also received a scholarship grant from MSD, JT, Nippon Boehringer Ingelheim, Takeda, Dainippon Sumitomo Pharma, Astellas Pharma, Daiichi-Sankyo, and Mitsubishi Tanabe Pharma. Kazuaki Nagashima received funding from MSD. Shizuka Kaneko received funding from Novartis Pharma and Novo Nordisk. Takashi Matsuoka received funding from Eli Lilly Japan and Novartis Pharma. Shimpei Fujimoto received funding from Takeda, Mitsubishi Tanabe Pharma, Novartis Pharma, Sanofi, MSD, Astellas Pharma, Eli Lilly Japan, Novo Nordisk, Sanwa Kagaku Kenkyusho, Kowa Company, Shionogi, Nippon Boehringer Ingelheim, AstraZeneca, Kyowa Hakko Kirin, and Dainippon Sumitomo Pharma. Shiro Hinotsu received funding from Sanofi. Takeo Nakayama served as a medical advisor for Asahi Kasei Pharma. No other potential conflicts of interest relevant to this article were reported.

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A hospital-based cross-sectional study to develop an estimation formula for 2-h post-challenge plasma glucose for screening impaired glucose tolerance☆

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ABSTRACT

Aims: To create and validate an estimation formula for 2-h post-challenge plasma glucose (2-hPG) as an alternative to oral glucose tolerance test (OGTT) for impaired glucose tolerance (IGT) screening.

Methods: 380 Japanese subjects (57.6% males, aged 58.5 (14.0); mean (SD) years) undergoing OGTT were included in this hospital-based cross-sectional study mainly at Kyoto University Hospital between 2000 and 2011. We determined the main predictive variables of 2-hPG from clinical variables and separated the subjects randomly into two groups: a derivation group to construct an estimation formula of 2-hPG on the basis of predictive variables and a validation group to evaluate the accuracy of the formula.

Results: Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) were highly correlated with 2-hPG measured by OGTT. Multiple linear regression analysis showed that estimated 2-hPG (e2-hPG) was calculated by the formula: e2-hPG = 1.66 × FPG (mmol/l) + 1.63 × HbA1c (%) − 10.11 (R^2, coefficient of determination = 60.2%). When the cut-off value was set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity, specificity, and negative predictive value (NPV) were 83.3%, 44.1%, and 74.3%, respectively. When the cut-off value was set lower (7.2 mmol/l), these values were 94.4%, 30.5%, and 85.7%, respectively. The area under the receiver operating characteristic (ROC) curve was 0.68.

Conclusions: This high-sensitive estimation formula may be a useful alternative to OGTT for IGT screening. For the levels ≤7.2 mmol/l, this formula may also be useful in cross-sectional study to identify people whose glucose tolerance is normal.

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1. Introduction

Impaired glucose tolerance (IGT) represents high risk not only for development of type 2 diabetes mellitus (DM) but also for cardiovascular disease [1–5]. A meta-analysis has shown that subjects with IGT have an annualized relative risk (95% confidence interval) for progression to DM of 6.35 (4.87–7.82) compared to those with normal glucose tolerance (NGT) [5]. Furthermore, it is known that lifestyle and pharmacological interventions for IGT are effective in preventing or delaying type 2 DM [6–9]. Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), Collaborative Analysis of Diagnostic Criteria in Asia (DECODA), and Funagata Diabetes study have shown a strong association between postprandial hyperglycemia such as that seen in IGT and cardiovascular risk [3,10,11]. Cardiovascular mortality in subjects with IGT is similar to that in type 2 DM and much greater than that in impaired fasting glucose (IFG) [12]. Thus, detection of IGT is critical for preventing type 2 DM and reducing diabetic complications.

The ''gold standard'' method for diagnosing IGT defined by 1998 World Health Organization (WHO) criteria uses the level of 2-h post-challenge plasma glucose (2-hPG) during oral glucose tolerance test (OGTT) [13]. However, it is difficult to implement this test in a large population due to time and expense requirements [14]. For this reason, alternative methods for identifying IGT without OGTT have been investigated. Neither fasting plasma glucose (FPG) nor hemoglobin A1c (HbA1c) can be used singly to predict IGT due to the low detection rate [15–18]; however, combined use of FPG and HbA1c has been shown to be more effective [19]. Age, gender and body mass index (BMI) also have effects on the accuracy of IGT screening with single use of FPG an HbA1c [17,20–23]. At this point in time, there is no validated estimation formula to screen IGT that takes the predictive variables into account.

We screened for predictive variables of 2-hPG in hospital-based Japanese subjects and were able to develop an estimation formula for 2-hPG based on these predictive variables. We also validated the derived estimation formula for IGT screening which would be available for clinical settings.

2. Subjects and methods

2.1. Subjects

Three hundred eighty Japanese subjects not taking oral hypoglycemic agents and undergoing 75 g OGTT were recruited in this cross-sectional study at the Department of Diabetes and Clinical Nutrition, Kyoto University Hospital and other hospitals during the period of December 2000 through October 2011. Inclusion criteria were: family history of type 2 DM, past history of gestational diabetes, more than 20 years old, BMI > 25 kg/m^2, positive result of urine glucose test or hyperglycemia at examination for regular medical checkup. Exclusion criteria were: history of type 1 DM, endocrine diseases, operations such as gastrectomy and pancreatectomy, treatment with medications known to affect glucose metabolism, and all conditions that might lead to misinterpretation of HbA1c, such as anemia. The study protocol was approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee and conducted according to the Declaration of Helsinki. Informed consent was obtained from all subjects.

2.2. Measurements

Physical variables (age, gender, height, body weight, BMI) and laboratory variables (plasma glucose, immunoreactive insulin (IRI), HbA1c) were taken. Each standard OGTT was administered according to the National Diabetes Data Group recommendations [24]. Blood samples for determination of blood glucose levels were collected at 0, 30, 60, 90, and 120 min after oral administration of 75 g glucose. As the index of insulin secretion, we used the insulinogenic index, the change in the ratio of insulin to glucose level during the first 30 min of OGTT: (IRI 30 min − fasting immunoreactive insulin (F-IRI))/(PG 30 min − FPG) [25,26].

2.3. Laboratory examination

PG was measured by glucose oxidase method using the Hitachi Automatic Clinical Analyzer 7170 (Hitachi, Tokyo, Japan). IRI was measured by two-site radioimmunoassay (Insulin Riabead II, Dainabot, Tokyo, Japan). HbA1c was measured using high performance liquid chromatography (HPLC) and is expressed as a National Glycohemoglobin Standardization Program (NGSP) equivalent value calculated by the formula: HbA1c (NGSP value) (%) = 1.02 × HbA1c (Japan Diabetes Society value) (%) + 0.25 [27]. The HbA1c measurements in International Federation of Clinical Chemistry (IFCC) units (mmol/mol) were also calculated.

2.4. Definitions

According to the 1998 WHO diagnostic criteria [13], the subjects were classified into the following four subgroups: NGT; FPG mmol/l $<$ 6.1 mmol/l and 2-hPG $<$ 7.8 mmol/l, IGT; FPG $<$ 7.0 mmol/l and 7.8 mmol/l $\leq$ 2-hPG $<$ 11.1 mmol/l, IFG; 6.1 mmol/l $\leq$ FPG $<$ 7.0 mmol/l and 2-hPG $<$ 7.8 mmol/l, DM: 7.0 mmol/l $\leq$ FPG or 11.1 mmol/l $\leq$ 2-hPG.

As shown in the supplemental table, sensitivity was defined as the proportion of subjects with IGT by OGTT who were predicted to have a positive result by the estimation formula: $\{a/(a+c)\} \times 100$ (%). Specificity was defined as the proportion of subjects without IGT who were predicted not to have IGT; $\{d/(b+d)\} \times 100$ (%). Positive predictive value (PPV) was defined as the proportion of subjects predicted to have IGT who were truly IGT by OGTT; $\{a/(a+b)\} \times 100$ (%). Negative predictive value (NPV) was defined as the proportion of subjects predicted not to have IGT who were truly not IGT by OGTT; $\{d/(c+d)\} \times 100$ (%). A receiver operating characteristic (ROC) curve was constructed by plotting sensitivity against the false-positive rate (100 − specificity) (%) over a range of cut-off values.

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2.5. Statistical analyses

Statistical analyses were performed according to the following steps.

(1) Background of the subjects: results were expressed as mean (standard deviation: SD or mean standard error: SE). Differences between the two groups were compared using the Student's *t*-test. *P* value $< .05$ (two-tailed) was considered as statistically significant.
(2) The relationship between two variables: the relationship between measured 2-h post-challenge plasma glucose (m2-hPG) and clinical variables was evaluated by scatter plot and Pearson's correlation coefficient (*r*).
(3) Derivation and validation: to avoid over-fitting of the estimation formula, two-step procedure was used. A total of 380 subjects were randomly divided into two groups at 1 to 1 ratio, a derivation group for constructing the estimation formula to screen IGT and a validation group without DM for evaluating the accuracy of the derived estimation formula.
(4) Construction of the estimation formula in the derivation group: higher values of correlation coefficient demonstrated in the previous step were regarded as predictive variables for m2-hPG, and the estimation formula of 2-hPG with these variables was then constructed by multiple linear regression analysis.
(5) Evaluation of the derived estimation formula in the validation group: the diagnostic characteristics such as sensitivity, specificity, PPV, and NPV of this derived estimation formula were calculated. The performance of the estimation formula was assessed by calculating the area under the ROC curve based on sensitivity and specificity [28]. In addition, we determined the adequate cut-off value by considering these values.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Characteristics of the subjects

Clinical characteristics of the subjects are shown in Table 1. Results of age and HbA1c are shown as mean (SD); the others are shown as mean (SE). Because the number of IFG ($n = 9$) was too small for analysis, we compared physical and metabolic

Table 1 – Characteristics of the subjects.

	NGT	IFG	IGT	DM	Total
Number (%)	126 (33.2)	9 (2.4)	106 (27.9)	139 (36.6)	380 (100)
Male (%)	60 (47.6)	6 (66.7)	50 (47.2)	103 (74.1)	219 (57.6)
Age (year)†	54.5 (15.5)	61.4 (15.5)	57.0 (13.3)	63.2 (11.6) **vs. NGT	58.5 (14.0)
BMI (kg/m^2)‡	23.5 (4.8)	26.1 (2.4)	25.9 (5.6) **vs. NGT *vs. DM	24.4 (3.5)	24.6 (4.7)
HbA1c (%)†	5.9 (0.6)	6.5 (0.6)	6.2 (0.5) ***vs. NGT	7.0 (0.6) ***vs. NGT ***vs. IGT	6.4 (0.7)
HbA1c (mmol/mol)	40.9 (6.1)	47.5 (6.3)	44.0 (5.2) ***vs. NGT	53.1 (6.5) ***vs. NGT ***vs. IGT	46.0 (8.0)
F-IRI (pmol/l)†	36.0 (24.8)	50.7 (32.6)	43.7 (28.1) *vs. NGT	41.7 (25.0) *vs. NGT	40.6 (26.2)
2-hIRI (pmol/l)†	222.3 (155.6)	354.7 (282.4)	351.9 (217.9) ***vs. NGT	274.2 (180.5) *vs. NGT **vs. IGT	282.7 (194.6)
FPG (mmol/l)†	5.1 (0.5)	6.5 (0.2)	5.5 (0.6) ***vs. NGT	7.0 (1.2) ***vs. NGT ***vs. IGT	6.0 (1.2)
2-hPG (mmol/l)†	6.2 (1.1)	6.8 (0.7)	9.4 (0.9) ***vs. NGT	14.6 (2.8) ***vs. NGT ***vs. IGT	10.2 (4.0)
Inslinogenic index‡	65.1 (38.4)	31.2 (24.2)	38.5 (24.6) ***vs. NGT	15.8 (6.5) ***vs. NGT ***vs. IGT	33.8 (17.9)

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; F-IRI, fasting immunoreactive insulin; 2-hIRI, 2-h immunoreactive insulin; FPG, fasting plasma glucose; 2-hPG, 2-h post-challenge plasma glucose; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; DM, diabetes mellitus; SD, standard deviation; SE, standard error.
* $P < .05$.
** $P < .01$.
*** $P < .001$.
† Data are described means (SD).
‡ Data are described means (SE).

variables among the three other groups (NGT, IGT, and DM). The total of mean age (SD) is 58.5 (14.0) years and 57.6% are males. Age of DM subjects is the highest ($P < .01$ vs. NGT) and BMI of IGT subjects is the highest ($P < .01$ vs. NGT and $P < .05$ vs. DM, respectively) among the three groups. HbA1c is significantly higher, while insulinogenic index is significantly lower in subjects with DM than in those with NGT and IGT. Glucose and plasma insulin levels during OGTT are given in the supplemental figure. For plasma glucose, subjects with NGT are those with 5.1 (0.5) mmol/l of FPG and 6.2 (1.1) mmol/l of 2-hPG (Supplemental Figure A). For subjects with IFG, FPG is 6.5 (0.2) mmol/l and for those with IGT, 2-hPG is 9.4 (0.9) mmol/l. For subjects with DM, FPG is 7.0 (1.2) mmol/l and 2-hPG is 14.6 (2.8) mmol/l. Early-phase insulin secretion shown in Supplemental Figure B is already decreased in the IGT stage as shown in the previous Japanese study [29].

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3.2. *Relationship between two variables*

We evaluated the relationship among all pairs of continuous variables using scatter plot and calculated Pearson's correlation coefficient. Using this procedure, we found the predictive variables for m2-hPG in this target population.

Fig. 1 shows the scatter plot of m2-hPG and FPG (Fig. 1A) and that of m2-hPG and HbA1c (Fig. 1B) in OGTT of all subjects. The correlation coefficient (r) between two variables is 0.74 and 0.67, respectively. Except for these two variables, there is no higher correlation coefficient than 0.5 between m2-hPG and the physical, metabolic variables.

3.3. *Construction of the estimation formula in the derivation group*

First, all subjects were randomly divided 1:1 into the derivation group and the validation group to avoid over-fitting.

At a stage prior to this, FPG and HbA1c were substantiated as main predictive variables for m2-hPG, then the estimation formula with these variables was constructed by using the multiple linear regression analysis in the derivation group. The obtained linear regression equation (estimation formula) is e2-hPG = 1.66 × FPG (mmol/l) + 1.63 × HbA1c (NGSP: %) − 10.11, or e2-hPG = 1.66 × FPG (mmol/l) + 0.15 × HbA1c (mmol/mol) − 6.61. R^2 (coefficient of determination) is 60.2%. Moreover, we analyzed to determine whether inclusion of other variables known to affect 2-hPG improved the accuracy of this formula. Even though other variables such as BMI, age, gender, and IRI are included in the regression model, R^2 remains substantially unchanged (data not shown). FPG and HbA1c are thus the best predictors of 2-hPG based on the linear regression model and we concluded the estimation formula of 2-hPG shown in Fig. 2 in this derivation group.

3.4. *Evaluation of the derived estimation formula in the validation group*

The accuracy of this estimation formula: diagnostic characteristics such as sensitivity, specificity, PPV, NPV, and the area under the ROC curve were calculated in the validation group. Table 2 shows the results of sensitivity, specificity, PPV, and NPV for every 0.2 mmol/l of e2-hPG in this group. When the cut-off value is set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity, specificity and NPV of this formula are 83.3%, 44.1%, and 74.3%, respectively. When the cut-off value is ≤7.8 mmol/l of e2-hPG, sensitivity is retained more than 80%, and when lowered to 7.2 mmol/l of e2-hPG, sensitivity, specificity, and NPV are 94.4%, 30.5% and 85.7%, respectively. These results are plotted in Fig. 3. In the validation group, the ROC curves obtained by calculating sensitivity and specificity at possible cut-off points of estimated 2-hPG are also shown in Fig. 3. The performance of the estimation formula was assessed by calculating the area under the ROC curve, which is 0.68.

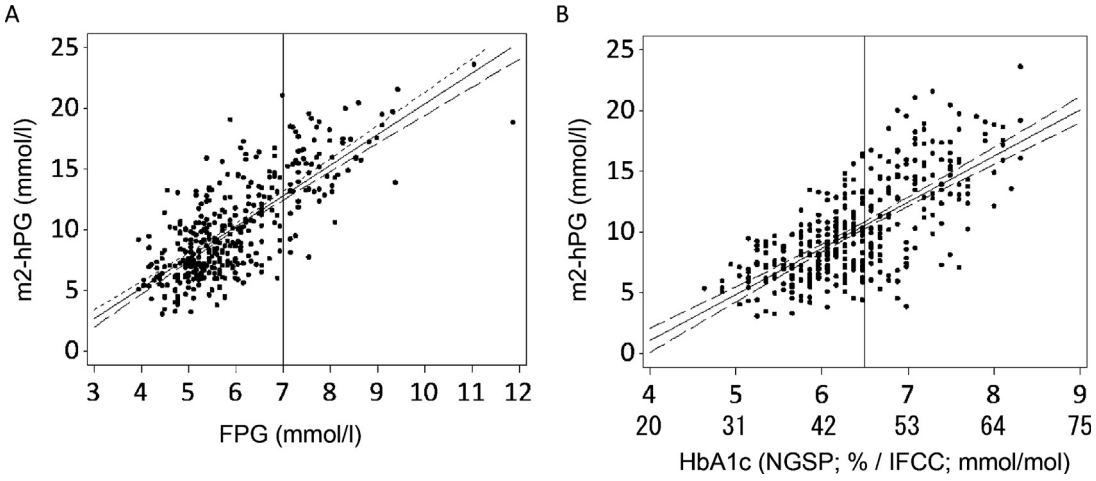

Fig. 1 – Scatter plot of measured 2-hPG (m2-hPG) and FPG in OGTT (A) and that of m2-hPG and HbA1c in OGTT (B); the correlation coefficient (r) = 0.74, 0.67, respectively.

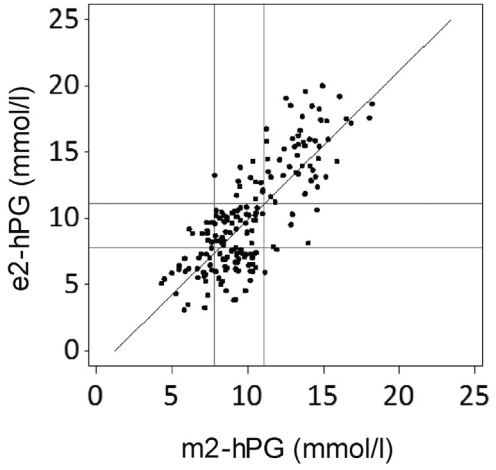

Fig. 2 – Scatter plot and the estimation formula of estimated 2h-PG (e2-hPG) in derivation group. e2-hPG = 1.66 × FPG (mmol/l) + 1.63 × HbA1c (%) − 10.11 (R^2 = 60.2%). e2-hPG = 1.66 × FPG (mmol/l) + 0.15 × HbA1c (mmol/mol) − 6.61 (R^2 = 60.2%).

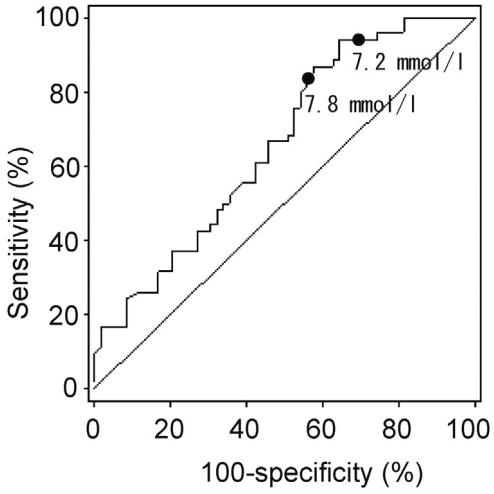

Fig. 3 – Receiver operating characteristic (ROC) curves obtained by calculating sensitivity and specificity at possible cut-off points of estimated 2-hPG in validation group. The horizontal axis shows the (100 − specificity) (%) and the vertical axis shows the sensitivity (%). When the cut-off value is set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity and specificity are 83.3% and 44.1%, respectively. When the cut-off value is set lowered to 7.2 mmol/l of e2-hPG, those are 94.4% and 30.5%, respectively. The area under the ROC curve is 0.68.

4. Discussion

In the present study, we found that the main predictive variables associated with m2-hPG are FPG and HbA1c from the data of 380 hospital-based Japanese subjects. We were able to develop a validated estimation formula for 2-hPG with these variables as an alternative to OGTT for IGT screening.

Studies have reported that lifestyle and pharmacological intervention for subjects with IGT can prevent or delay the onset of type 2 DM [6–9]. Detection and early intervention for these high-risk individuals is critical for preventing type 2 DM and reducing diabetic complications. Even though OGTT is the ''gold standard'' method for diagnosing IGT, in a large population that method is time-consuming and expensive [14].

Some studies have investigated alternative methods for evaluating IGT without performing OGTT [15–23]. The single use of FPG or HbA1c is not suitable for IGT screening because of the low detection rate [15–18]. It was reported in a systematic review that for detecting IGT by HbA1c or FPG separately, that sensitivity is around 50% [16]. Indeed, in our result, with single use of FPG or HbA1c, R^2 was 56.2% and 48.3%, respectively (Fig. 1), while using the estimation formula with both FPG and HbA1c, R^2 was 60.2% (Fig. 2) for IGT screening. This result is compatible with the previous study recommending the combined use of these two variables to be more effective than single use for detecting IGT [19]. But this study did not elucidate the influence of each of the variables on 2-hPG.

Table 2 – Summary of sensitivity, specificity, PPV, and NPV for every 0.2 mmol/l of estimated 2-hPG (e-2hPG) in the validation group.

Cut-off value of e2-hPG (mmol/l)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
6.8	96.3	23.7	53.6	87.5
7.0	96.3	25.4	54.2	88.2
7.2	94.4	30.5	55.4	85.7
7.4	87.0	37.3	56.0	75.9
7.6	87.0	40.7	57.3	77.4
7.8	83.3	44.1	57.7	74.3
8.0	70.4	47.5	55.1	63.6
8.2	66.7	52.5	56.3	63.3
8.4	61.1	57.6	56.9	61.8
8.6	53.7	62.7	56.9	59.7
8.8	50.0	66.1	57.4	59.1

PPV, positive predictive value; NPV, negative predictive value.

Caucasians generally have higher BMI and insulin resistance is important in progression from NGT to IGT [30], while Asians including Japanese are generally less obese and have higher insulin sensitivity than Caucasians. Several previous studies reported that BMI is a helpful factor for IGT screening [17,20–23]. High BMI (>27 or >30 kg/m^2) is associated with higher prevalence of IGT compared to that with BMI < 25 kg/m^2. Hiltunen et al. reported that higher BMI (>30 kg/m^2) was the best predictor of IGT in a Finland population-based study and Saydah SH et al. reported that BMI (>30 kg/m^2) and age in addition to FPG or HbA1c can be used to improve the sensitivity for detecting IGT without OGTT among U.S. populations [20,23]. Contrary to these reports, we did not find a high correlation between 2-hPG and BMI ($r = 0.03$). The proportion of obesity of these studies is high, the ratio of BMI > 27 kg/m^2 and >30 kg/m^2 are 53% and 24%, respectively [20,23], while in our study the mean (SD) of BMI was 24.6 (4.7) kg/m^2 and the ratio of obese subjects with BMI > 30 kg/m^2 are only 1%. It was reported previously that the difference with or without the obesity (BMI > 25 kg/m^2) did not contribute to IGT screening in Japanese [21]. The BMI used in the study was similar to that in our study (BMI: 23–25 kg/m^2). On the other hand, insulin secretion rather than insulin resistance is a more significant factor in progression from NGT to type 2 DM via IGT in Asian diabetes [29,31–35]. Indeed, in the present study insulin secretion is decreased gradually from NGT via IGT to type 2 DM (65.1, 38.5, 15.8, respectively) as in other previous reports in Asian diabetes [31,35] (Table 1). Taken together, the discrepancy of the correlation may be due to the ethnic differences such as BMI and insulin secretory capacity. The variables affecting 2-hPG during OGTT might differ among ethnic populations and require a different estimation formula and adequate cut-off value to identify IGT. It is also reported that age has an effect on the accuracy of IGT screening [22]. In our study, however, there was low correlation between 2-hPG and age ($r = 0.24$). The reason may be the different methods of analysis. We considered age from 20 to 89 years as a continuous variable rather than as a categorical one with relatively narrow age. In addition, gender was not an independent predictive variable for 2-hPG and even though included in the regression model, R^2 remains substantially unchanged in our study (data not shown).

Generally, the performance of a screening test depends on the cut-off value and it is rare to have both high sensitivity and specificity. The priority in this trade-off is determined by the characteristics of the condition to be diagnosed [36,37]. In the case of IGT, mis-identifying IGT subjects as normal (false negatives) is more critical than classifying healthy subjects as abnormal (false positives), since these subjects are at high risk for cardiovascular diseases as well as diabetes and its complications. Thus, a screening test for IGT should prioritize high sensitivity to decrease the false-negatives. As summarized in Table 2, when the cut-off value was set to the diagnostic criteria of IGT, 7.8 mmol/l of e2-hPG, sensitivity of this formula was 83.3%. However, even with this cut-off value, NPV still remained 74.3%. If the cut-off value was lowered to 7.2 mmol/l, NPV was up to 85.7% with 94.4% sensitivity. When a screening test has high sensitivity, subjects having a negative result can be judged as negative with high precision [36–39]. The rule of SnNout states that if a screening test has high sensitivity (Sn), a negative result (N) rules out (Out) the target disorder, which describes IGT in our study. In accord with this theory, using our high-sensitive estimation formula for IGT screening and with the cut-off value set to 7.2 mmol/l of e2-hPG with 94.4% sensitivity, the subjects with e2-hPG ≤ 7.2 mmol/l were ruled out of the diagnosis of IGT. Thus, further OGTT to diagnose whether or not they have IGT may not be necessary for these low risk subjects.

Our study has several limitations. One is the high prevalence of type 2 DM subjects in our hospital-based study. It is reported that the prevalence of type 2 DM varies across studies, in hospital-based studies ranging from 10 to 44% and in community-based studies ranging from 6.2 to 7.4% [16]. While the proportion of subgroups in OGTT would affect the efficacy of the estimation formula, there are at present no established data of general population-based or hospital-based studies. Thus, no comparisons are possible between our results with previous findings. Another limitation is screening bias because it is a cross-sectional study. There are no definite inclusion criteria—they depend on the individual judgment of each doctor. Our results regarding sensitivity, specificity, and cut-off value are internally validated, but it remains to be determined whether these findings apply to other populations: generation-based or higher BMI like Caucasian and so on. Therefore further studies are required to validate in the broader population.

In conclusion, our high-sensitivity estimation formula based on FPG and HbA1c may be useful in screening for IGT. More than 80% sensitivity of this formula was preserved at ≤7.8 mmol/l of e2-hPG in this hospital-based study. In addition, when the levels of e2-hPG are ≤7.2 mmol/l, this estimation formula can be used to identify subjects with normal glucose tolerance.

Conflict of interest

The authors declare that they have no conflict of interest.

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