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Sitagliptin versus mitiglinide switched from mealtime dosing of a rapid-acting insulin analog in patients with type 2 diabetes: a randomized, parallel-group study

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ABSTRACT

Purpose: We determined the feasibility of substituting sitagliptin or mitiglinide for bolus insulin injection therapy in patients with type 2 diabetes.

Methods: 60 patients with type 2 diabetes were enrolled and randomized to switch from mealtime dosing of a rapid-acting insulin analog to either sitagliptin or mitiglinide for 16 weeks.

Results: Body weight, body mass index, and waist circumference decreased significantly in both groups at the end of the study. Mitiglinide significantly increased fasting plasma glucose (FPG) levels at the end of the study from 146.5±36.3 to 168.0 ±38.8 mg/dL, whereas sitagliptin did not affect FPG. Glycated hemoglobin (HbA1c) and 1,5-anhydroglucitol increased significantly in both groups. The C peptide immunoreactivity (CPR) responses after arginine were diminished in both groups. γ-GTP and triglycerides increased, and high-density lipoprotein cholesterol and adiponectin decreased, in the sitagliptin group, but not in the mitiglinide group. Mean Diabetes Treatment Satisfaction Questionnaire scores improved significantly in both groups. Patients whose mean total daily doses of rapid-acting insulin analog were 16.6 and 17.8 units were switched to sitagliptin and mitiglinide, respectively, without a change in the HbA1c level. Total insulin doses/body weight predicted changes in HbA1c only in the sitagliptin group, but not in the mitiglinide group. Use of >0.27 IU/kg of a rapid-acting insulin analog predicted an increase in HbA1c after switching to sitagliptin. The CPR index (CPI) was also a predictor for a change in HbA1c in the sitagliptin group, but not in the mitiglinide group; patients with a CPI<1.4 developed a worse HbA1c after switching to sitagliptin.

Conclusions: Sitagliptin may predominantly act on FPG, whereas mitiglinide may act on postprandial plasma glucose to achieve glycemic control after switching from a bolus insulin regimen. Additional therapy to sitagliptin or mitiglinide is clearly required to obtain equivalent glycemic control in patients using a higher dose of insulin.

Trial registration number: (UMIN 000007051)

Key messages

- This is the first report showing the feasibility of substituting oral hypoglycemic agents for insulin injection therapy in an open-label randomized, parallel-group study. The predictive variable for a change in glycated hemoglobin (HbA1c) was total insulin dose before switching.
- Patients whose mean total daily doses of rapid-acting insulin analog were 16.6 and 17.8 units were switched to sitagliptin and mitiglinide, respectively, without a change in the HbA1c level. Use of >0.27 IU/kg of a rapid-acting insulin analog predicted an increase in HbA1c after switching to sitagliptin.
- Sitagliptin, but not mitiglinide, may exert unique pleiotropic effects on fatty acid composition. After the switch from insulin, sitagliptin significantly decreased the Δ5 desaturase, whereas it significantly increased the Δ6 desaturase.
- Patients with a C peptide immunoreactivity index (CPI) <1.4 had worse HbA1c levels after switching to sitagliptin. Our study is the first to prospectively demonstrate the usefulness of the CPI for "tailor-made" diabetic medicine.

INTRODUCTION

As the population with diabetes increases, the number of individuals receiving insulin injections increases proportionally. Rapid-acting insulin analogs have been particularly effective at targeting postprandial hyperglycemia as well as nadir fasting plasma glucose (FPG).[1–3] In contrast, excess insulin/insulin-like growth factor signaling accelerates cellular aging by negatively regulating FOXO transcription factors.[4] Aging phenotypes include cancer and dementia. The risk for liver cancer increases particularly in patients with diabetes undergoing insulin treatment.[5–7] Several studies have identified hyperinsulinemia as a risk factor for

accelerated cognitive decline and dementia.[8–10] Indeed, the risk of dementia is highest in patients with diabetes treated with insulin.[11–13] Insulin injection therapy is also associated with pain and places a heavy physical, mental, and financial burden on patients. Similarly, recent large-scale clinical trials have suggested that intensive antidiabetic therapies that cause unnecessary hyperinsulinemia do not result in satisfactory cardiovascular outcomes in patients with type 2 diabetes and may cause hypoglycemia and weight gain.[14]

One possible solution for this paradox came from the launch of incretin-based agents because they avoid unnecessary hyperinsulinemia and thereby avoid hypoglycemia and weight gain. Sitagliptin and mitiglinide are major agents for switching from insulin injections. Sitagliptin increases insulin secretion and decreases glucagon concentration in a glucose-dependent manner.[15] Its use results in a lower incidence of hypoglycemia compared with that of other oral hypoglycemic agents (OHAs).[16][17] However, mitiglinide provokes rapid and short-acting insulin secretion that improves postprandial hyperglycemia and mimics normal physiological insulin secretion and glucose metabolism in healthy individuals. Owing to its shorter duration of action, mitiglinide has a lower risk of hypoglycemia compared with other insulin secretagogues.[18]

From the perspective of switching from insulin treatment to an OHA, it is prudent to carefully consider the inclusion criteria. This approach may improve blood sugar control in patients with diabetes and help reduce the overall cost of medical care. Additionally, it remains unclear what clinical features of patients, including diabetes duration, dose of insulin, insulin secretory capacity, body composition, and fatty acid composition, are associated with changes in glycated hemoglobin (HbA1c) after switching from a bolus insulin regimen to an OHA. For these reasons, we determined the feasibility of substituting an OHA for insulin injection therapy in patients with type 2 diabetes.

METHODS
Overview
This was a randomized, parallel-group study conducted on Japanese patients. This study was designed in accordance with the principles stated in the Declaration of Helsinki, and the protocol was reviewed and approved by the Ethics Committee of Kanazawa University Hospital, Ishikawa, Japan. Patients provided written informed consent before participation.

Sixty patients with type 2 diabetes and on rapid-acting insulin injection therapy were recruited from our Department of Disease Control and Homeostasis from May 2010 to July 2011. This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry, number +000007051.

Patient eligibility
Inclusion criteria were: (1) males and females with type 2 diabetes (age, >20 years); (2) rapid-acting insulin dosage <60 units/24 h; and (3) moderately controlled diabetes with a change in HbA1c<3% in the 12 weeks before screening. We used this criterion according to the previous clinical trials, in which the inclusion criteria involve a 3–4.5% range of HbA1c. For example, the LEAD-1 SU study included patients with type 2 diabetes with HbA1c 7.0–11.0% or 7.0–10.0%.[19] Another study included patients who met the following inclusion criteria during the screening period: HbA1c 7–11.5% at 4 weeks before randomization, HbA1c 7–11% at 1 week before randomization.[20] Accordingly, we maximally allowed a <3% change in HbA1c for 12 weeks before screening. Exclusion criteria were: (1) hypersensitivity or contraindication to mitiglinide or sitagliptin; (2) a history of type 1 diabetes or a history of ketoacidosis; (3) experienced repeated episodes of unexplained hypoglycemia as defined by an FPG or without symptoms of hypoglycemia or <60 mg/dL with symptoms of hypoglycemia; (4) concomitantly suffering from infection or planning to have surgery; (5) treatment with a mitiglinide or sitagliptin within 12 weeks before screening; (6) concomitant corticosteroid therapy; (7) poorly controlled diabetes (with ketoacidosis or with an increase in HbA1c>3% in the 12 weeks before screening); (8) undergoing dialysis, and serum creatinine >2.5 mg/dL in men or >2.0 mg/dL in women; (9) alanine aminotransferase and/or aspartate aminotransferase (AST) levels more than 2.5-fold the upper limit of normal; (10) poorly controlled hypertension, systolic blood pressure >160 mm Hg, or diastolic blood pressure >100 mm Hg; (11) currently and/or previously suffering from heart failure; (12) severe retinopathy; (13) malignancy on active therapeutic regimen or without complete remission or cure; (14) pregnancy or breast feeding; and (15) some barrier to participation in the study, as assessed by the investigators.

Participants
Efficacy end points
The primary efficacy end point was the change in FPG from baseline to week 16. The secondary end point assessed at week 16 was the change in HbA1c from baseline. Other end points included blood 1,5-anhydroglucitol, fasting lipids, and insulin. The C peptide immunoreactivity (CPR) index (CPI) was calculated using the formula: $[100 \times \text{fasting CPR (ng/mL)}]/[18 \times \text{FPG (mm)}]$.[21] C peptide and insulin levels were determined by an immunoenzymometric assay using Tosoh kits (Shunan, Japan). The lower limit of quantification for CPR was 0.2 ng/mL. The intra-assay and inter-assay coefficients of variation were <6%. Glucose and HbA1C were measured by standard methods. The results of a physical examination, vital signs (blood pressure), body weight, and laboratory evaluations, including

hematology, serum chemistry, and urinalysis, were recorded throughout the study.

Serum fatty acid levels were measured as a secondary outcome. A serum sample (approximately 0.2 mL) and 2 mL chloroform-methanol (2:1) were placed in a Pyrex centrifuge tube, homogenized with a Polytron homogenizer (PCU-2-110; KINEMATICA GmbH, Lucerne, Switzerland), and centrifuged at 3000 rpm for 10 min. An aliquot of the chloroform-methanol extract was transferred to another Pyrex tube and dried under a nitrogen gas stream. The dried sample was dissolved in a 100 µL 0.4 M potassium methoxide methanol/14% boron trifluoride-methanol solution, and the fatty acid concentration was measured at SRL Inc. by gas chromatography (Shimizu GC 17A, Kyoto, Japan). The Δ5 desaturase (D5D) activity index and the Δ6 desaturase (D6D) activity index were expressed as the arachidonic acid to dihomo-γ-linolenic acid ratio and the γ-linolenic acid ratio to the linoleic acid ratio in blood, respectively.

Safety and tolerability were assessed by reviewing several safety parameters. Key safety parameters included general adverse experiences (AEs), treatment discontinuations, hypoglycemic events, and hyperglycemic events, as well as other parameters of interest, such as body weight and urinary ketones. AEs were monitored throughout the study and were rated by the investigators for intensity and their relationship to the study drug. AEs with an onset date up to 2 weeks after concluding treatment were evaluated in person.

A computer-generated dynamic randomization sequence assigned participants in a 1:1 ratio to treatment in the sitagliptin or mitiglinide group to adjust for demographic differences (age, insulin dose, and HbA1c) between the agents' groups. The study continued in an open-label fashion for an additional 16 weeks as described. Combination therapy was initiated on the day on which insulin injection therapy was completely withdrawn. The concomitantly used OHAs and medications other than hypoglycemic agents were continued after the switch. Patients remained on stable doses of the medications during the study period. The investigators did not use rescue medication such as insulin or sulfonylureas at any time after randomization even if patients did not achieve a satisfactory therapeutic effect.

All patients and responsible guardians underwent 1 h of nutritional counseling with an experienced dietician before the study. In addition, all patients were given a standard calorie diet (30 kcal/kg/day; 50–60% carbohydrate, 20–30% fat, and 15–20% protein) and exercise (5–6 metabolic equivalent estimations for 30 min daily) counseling before the study.

Arginine-stimulation test

The arginine-stimulation test has been demonstrated to be a valid method for evaluating residual β-cell function, even during periods of hyperglycemia.[22] We previously showed that arginine-evoked insulin secretion predicts the requirement for basal insulin replacement in patients with type 2 diabetes.[1] In the present study, we tested the hypothesis whether the β-cell function evaluated with the arginine-stimulation test predicts the effects of sitagliptin or mitiglinide on HbA1c after switched from insulin therapy. Patients were kept still for 30 min after an overnight fast, and CPR were assessed at the preloading baseline (0 min). Arginine (30 g) was administered intravenously by infusing a 10% L-arginine hydrochloride solution over 30 min. Blood was collected at seven time points: preloading (0 min) and 15, 30, 45, 60, 90, and 120 min after arginine loading. Circulating CPR was measured at each time point and used to construct an arginine-stimulated time-response curve. The values of the area under the concentration-time curve for CPR (AUCCPR) between time 0 and 120 min were calculated using the trapezoidal rule and indicate the insulin-secreting response to arginine. The value of Arginine ΔCPR was defined as the difference between maximal and basal levels of CPR during the arginine test.

Lipid meal test

Participants ingested a liquid meal (750 kcal, 500 mL; Pulmocare, Abbott Japan, Tokyo, Japan) containing 53 g carbohydrate, 47 g lipid (including 20% medium chain triglycerides), and 31 g protein,[23] which has the highest carbohydrate and fat contents among the liquid test meals available at our hospital, after an overnight fast. Venous blood was obtained before and 30, 60, 120, and 180 min after ingestion, and plasma glucose and triglycerides were measured. Patients were instructed not to take sitagliptin or mitiglinide before the test. The AUCCPR values between time 0 and 180 min were calculated using the trapezoidal rule and indicate the insulin-secreting responses to the lipid meal test. The value of the lipid meal test ΔCPR was defined as the difference between the maximal and basal levels of CPR during the lipid meal test.

Treatment satisfaction

Treatment satisfaction was a secondary outcome and was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)[24–26] at baseline and at the end of the study. The overall treatment satisfaction score was calculated as the sum of DTSQ item 1, Satisfaction; item 4, Convenience; item 5, Flexibility; item 6, Understanding; item 7, Recommend to others; and item 8, Wish to continue. Item 2, perceived hyperglycemia frequency, and item 3, perceived hypoglycemia frequency were treated as separate variables. The quality of life (QOL) instrument was not designed to measure treatment satisfaction related to the device.

Statistical analysis

Sample size was estimated to be 26 in each group to detect a 31.6 and 15.6 mg/dL decreased in FPG in the sitagliptin group[27] and mitiglinide group,[28] respectively, with an α of 0.05 (one tailed) and a β of 0.20 with 80%

power and a standardized effect size of 25. To take the dropout rate of 15% into account, the aim was to include 60 participants. Two analyses were conducted. Data that were missing for participants who discontinued the study were replaced with baseline data for the intention-to-treat analysis. In the second analysis, the only data included were from participants who completed the study (through the 16-week follow-up period). We performed a completed case analysis rather than an intention-to-treat analysis because there were few dropouts and their reasons for dropping out were unrelated to baseline values or their responses. Data are expressed as means±SD. The SPSS (V.22.0; SPSS, Chicago, Illinois, USA) was used for all the statistical analyses. Parameters were analyzed using the Wilcoxon signed-rank test for the intergroup comparison, and Mann-Whitney's U test for the internal group comparison. Associations between variables were assessed using Spearman's rank correlation coefficient. p Values <0.05 were considered as statistically significant.

RESULTS
Baseline metabolic parameters
Patients were recruited between May 2010 and July 2011, with the follow-up continuing for 16 weeks thereafter. Sixty patients consented to participate in the study and were screened and randomized (see online supplementary figure S1). The mean age of all participants was 63.5±12.0 years, mean average diabetes duration was 9.7 ±9.2 years, mean average insulin dose was 21.3±8.8 U/ 24 h, mean average duration of insulin use was 4.3 ±5.6 years, and mean body mass index (BMI) was 24.3 ±4.2 kg/m^2 (see online supplementary table S1). FPG, HbA1c, and CPR immediately before the switch were 147.8±36.3 mg/dL, 6.8±0.7%, and 1.9±0.8 ng/mL, respectively.

The groups were generally well balanced with respect to baseline demographics and disease characteristics, except for the serum creatinine level (sitagliptin creatinine (Cre) 0.69±0.19, mitiglinide Cre 0.81±0.23, p=0.036).

Of the 60 patients enrolled, 3 dropped out after the switch. The first dropout case was in the mitiglinide group (age, 70 years). The participant had returned to insulin therapy and developed a subconjunctival hemorrhage 8 weeks after the switch; the second case was in the sitagliptin group (age, 69 years). The participant voluntarily returned to insulin treatment and withdrew consent 3 days after the switch; and the third case (age, 57 years) returned to insulin therapy and became hyperglycemic 12 weeks after the switch (see online supplementary figure S1).

Clinical outcomes
FPG, which was the primary study outcome, increased significantly at the end of the study from 146.5±36.3 to 168.0±38.8 mg/dL in the mitiglinide group, but did not change in the sitagliptin group.

Body weight, BMI, and waist circumference decreased significantly compared with baseline values in both groups at the end of the study (table 1). γ-GTP and triglycerides increased, and high-density lipoprotein cholesterol and adiponectin decreased, in the sitagliptin group, but not in the mitiglinide group. Sitagliptin increased the CPI, whereas mitiglinide significantly decreased the CPI.

The CPR responses after arginine were diminished in both groups. We investigated the liquid meal test results before and after switching to an OHA from insulin. The AUC CPR during the lipid meal test decreased significantly in the sitagliptin group when the participants switched from insulin.

Systolic blood pressure, blood urea nitrogen, AST, total cholesterol, small dense low-density lipoprotein, and tumor necrosis factor α had not changed significantly in either group at the end of the study.

Changes in plasma fatty acid composition
Sitagliptin significantly increased levels of lauric acid, myristic acid, γ-linolenic acid, α-linolenic acid, eicosatrienoic acid, dihomo-γ-linolenic acid, and erucic acid, while mitiglinide had no effect (table 2). As a result, sitagliptin significantly decreased D5D, whereas it significantly increased D6D. Mitiglinide did not affect D5D or D6D. Levels of lauric acid, eicosatrienoic acid, and dihomo-γ-linolenic acid increased significantly in the sitagliptin group compared with the mitiglinide group (table 2).

Treatment satisfaction
The mean DTSQ scores for the sitagliptin and mitiglinide groups were 24.2±6.7 and 22.3±1.6, respectively, at baseline and 29.6±4.5 and 28.4±1.3 respectively, at the end of the study (table 3). No significant differences were observed in the change in treatment satisfaction scores between groups (sum of items 1, 4, 5, 6, 7, and 8) or for the changes in perceived frequency of hyperglycemia (item 2) or hypoglycemia (item 3) at the end point (table 3).

Factors associated with improved HbA1c
We evaluated the correlation between factors and the change in HbA1c in a univariate analysis (see online supplementary table S2). Diabetes duration and use of insulin, physical balance, and fatty acid composition were not predictors of a change in HbA1c. Total insulin doses before switching from mealtime bolus insulin monotherapy to either sitagliptin or mitiglinide predicted changes in HbA1c in both groups. Patients whose mean total daily doses of rapid-acting insulin analog were 16.6 and 17.8 units were switched to sitagliptin and mitiglinide, respectively, without a change in the HbA1c level (see online supplementary figure S2). Total insulin doses/body weight predicted changes in HbA1c only in the sitagliptin group, but not in the mitiglinide group, whereas body weights did so only in the mitiglinide

Table 1 Baseline patient characteristics and changes after 16 weeks

	Sitagliptin			Mitiglinide			
	Before	After	p Value*	Before	After	p Value*	p Value†
Body weight (kg)	62.8±11.6	61.5±11.5	0.008	63.1±15.4	61.7±14.9	0.006	0.900
Body mass index (kg/m^2)	24.6±3.8	24.1±3.6	0.007	24.2±4.6	23.7±4.5	0.003	0.968
Waist circumference (cm)	88.0±11.1	86.1±10.0	0.025	87.6±14.1	85.8±12.9	0.001	0.999
Systolic blood pressure (mm Hg)	127.8±17.0	131.7±14.4	0.258	123.0±11.6	127.2±16.6	0.209	0.953
Fasting plasma glucose (mg/dL)	145.2±28.2	142.7±25.6	0.616	146.5±36.3	168.0±38.8	0.032	0.033
HbA1c (%)	6.6±0.5	7.2±0.9	0.000	7.0±0.8	7.9±1.5	0.000	0.153
BUN (mg/dL)	15.6±4.5	14.7±3.0	0.250	16.8±5.2	16.6±6.3	0.821	0.579
Cre (mg/dL)	0.69±0.19	0.68±0.19	0.742	0.81±0.24	0.78±0.24	0.030	0.166
Serum aspartate aminotransferase (IU/L)	23.2±7.2	24.8±9.5	0.279	30.0±20.1	27.3±17.0	0.414	0.236
Serum alanine aminotransferase (IU/L)	24.1±14.6	27.8±9.5	0.076	33.2±21.8	31.8±21.1	0.705	0.222
Plasma γ-glutamyltransferase (IU/L)	32.2±17.0	39.5±24.8	0.013	31.9±20.9	30.8±18.1	0.752	0.060
Total cholesterol (mg/dL)	182.5±30.1	182.6±32.4	0.979	181.6±23.8	177.6±22.5	0.341	0.485
Triglycerides (mg/dL)	113.3±48.3	168.4±46.2	0.022	107.1±46.3	116.1±49.6	0.228	0.060
HDL-C (mg/dL)	64.9±34.1	52.5±13.9	0.045	55.6±17.2	54.6±15.5	0.479	0.072
sdLDL (mg/dL)	32.9±13.9	36.8±17.0	0.159	27.9±8.2	28.2±10.0	0.827	0.255
Fasting serum insulin (IU/L)	10.0±6.6	8.3±5.7	0.517	8.9±8.0	9.1±10.3	0.879	0.118
CPR (ng/mL)	1.8±0.7	2.1±0.8	0.079	2.0±0.8	1.9±0.8	0.529	0.638
Arginine ΔCPR (ng/mL)	2.8±1.4	2.3±1.5	0.049	2.7±1.6	2.4±1.8	0.028	0.203
Arginine AUC CPR×10^2	4.6±1.6	4.4±2.0	0.587	4.7±2.1	4.6±2.1	0.778	0.731
Lipid meal test ΔCPR (ng/mL)	4.9±2.4	4.3±1.3	0.109	5.1±2.6	4.6±2.8	0.166	0.954
Lipid meal test AUC CPR×10^2	8.7±3.6	8.1±3.1	0.038	9.2±3.6	8.5±0.4	0.216	0.870
1,5-anhydroglucitol (mg/mL)	12.6±6.4	9.5±5.3	0.001	11.7±6.7	8.2±7.3	0.000	0.736
Leptin (ng/mL)	8.7±6.5	8.5±7.1	0.855	10.5±13.4	8.9±11.0	0.082	0.215
Adiponectin (mg/mL)	4.5±3.9	4.0±3.4	0.019	5.0±4.4	4.4±3.1	0.138	0.904
TNF-α (pg/mL)	2.9±1.7	1.6±1.7	0.267	2.1±1.9	2.0±1.6	0.801	0.325
HOMA-b	44.6±28.9	38.0±25.0	0.226	49.0±23.5	44.5±28.4	0.351	0.773
CPI	1.3±0.5	1.4±0.6	0.052	1.5±0.7	1.2±0.7	0.021	0.003

Data are means±SD.
*p Value for the intragroup comparison (baseline vs 16 weeks).
†p Value for the intergroup comparison (change from baseline between groups).
AUC, area under the curve; BUN, blood urea nitrogen; CPI, C peptide immunoreactivity index; CPR, C peptide immunoreactivity; Cre, creatinine; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment of insulin resistance; sdLDL, small dense low-density lipoprotein; TNF, tumor necrosis factor.

group, but not in the sitagliptin group (see online supplementary table S2). Use of >0.27 IU/kg of a rapid-acting insulin analog predicted an increase in HbA1c after switching to sitagliptin (see online supplementary figure S2).

The CPI was also a predictor for a change in HbA1c in the sitagliptin group, but not in the mitiglinide group; patients with a CPI<1.4 developed a worse HbA1c after switching to sitagliptin (see online supplementary figure S3). Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) levels did not predict a sitagliptin-mediated improvement in glycemic control. Changes in HbA1c in the mitiglinide group were negatively associated with changes in body weight and BMI.

DISCUSSION
This is the first report showing the feasibility of substituting an OHA for insulin injection therapy in an open-label randomized, parallel-group study. Our results show that FPG increased significantly in participants receiving mitiglinide, whereas no changes were observed in those administered sitagliptin. Mealtime bolus insulin monotherapy was superior to sitagliptin and mitiglinide for controlling HbA1c. Sitagliptin acted on FPG, whereas mitiglinide may act on the postprandial plasma glucose level to achieve a similar HbA1c after the switch from a bolus insulin regimen.

The majority of patients with type 2 diabetes treated with insulin have difficulty achieving or maintaining target glycemic control without an associated weight gain.[29] In this study, body weight, BMI, and waist circumference decreased significantly in both OHA groups after the switch from insulin. OHAs are more effective than bolus insulin monotherapy for maintaining weight in patients with type 2 diabetes at high risk for cardiovascular disease. We did not show a positive effect of OHAs on lipid profiles or blood pressure control. This could

Table 2 Changes in plasma fatty acid composition

	Sitagliptin		p Value*	Mitiglinide		p Value*	p Value†
	Before	After		Before	After		
C12:0 (lauric acid)	1.6±1.0	2.7±2.2	0.011	1.7±1.2	1.7±0.7	0.988	0.024
C14:0 (myristic acid)	23.7±9.8	32.3±17.5	0.015	24.9±12.5	26.3±9.2	0.586	0.083
C16:0 (palmitic acid)	707.9±182.1	779.3±322.1	0.212	707.4±129.9	680.0±125.6	0.270	0.114
C16:1n-7 (palmitoleic acid)	71.9±27.5	78.4±37.1	0.316	75.8±37.8	72.6±40.1	0.521	0.233
C18:0 (stearic acid)	213.0±42.9	232.8±86.2	0.244	204.0±30.3	197.9±31.9	0.269	0.148
C18:1n-9 (oleic acid)	644.2±245.2	747.8±405.7	0.151	606.9±125.6	607.0±142.6	0.997	0.165
C18:2n-6 (linoleic acid)	818.7±178.1	845.0±279.2	0.514	781.0±151.6	772.4±165.3	0.746	0.468
C18:3n-6 (γ-linolenic acid)	10.0±4.7	11.6±6.5	0.022	9.1±4.5	9.3±3.8	0.805	0.159
C18:3n-3 (α-linolenic acid)	26.1±11.3	35.8±26.7	0.029	23.8±8.6	25.1±10.9	0.487	0.073
C20:0n-6 (arachidic acid)	7.1±1.4	7.5±2.4	0.337	7.2±1.1	6.9±1.1	0.083	0.145
C20:1n9 (eicosenoic acid)	5.8±2.5	6.8±4.7	0.290	5.6±2.8	5.1±1.1	0.329	0.163
C20:2n6 (eicosadienoic acid)	5.9±1.7	6.3±2.2	0.332	5.7±1.3	5.6±1.3	0.637	0.280
C20:3n9 (eicosatrienoic acid)	2.2±1.2	2.6±1.4	0.012	2.0±1.1	1.8±1.0	0.436	0.027
C20:3n-6 (dihomo-γ-linolenic acid)	35.8±11.3	39.6±14.6	0.030	37.7±12.2	35.7±10.2	0.248	0.018
C20:4n-6 (arachidonic acid)	189.0±41.0	177.6±53.8	0.065	178.7±32.1	163.7±23.2	0.016	0.663
C20:5n-3 (eicosapentaenoic acid)	73.0±30.2	70.1±32.2	0.579	78.8±39.9	73.2±42.7	0.511	0.783
C22:0 (behenic acid)	18.3±3.7	17.9±5.4	0.583	18.4±4.0	17.8±4.7	0.269	0.836
C22:1n-9 (erucic acid)	1.5±0.5	1.8±0.9	0.047	1.6±0.6	1.8±0.5	0.121	0.674
C22:4n-6 (docosatetraenoic acid)	5.0±1.6	5.4±2.3	0.182	4.7±1.4	4.6±1.5	0.588	0.154
C22:5n-3 (docosapentaenoic acid)	21.1±5.7	23.1±9.2	0.148	21.3±6.9	21.5±9.3	0.921	0.352
C22:6n-3 (docosahexaenoic acid)	156.0±33.1	149.8±37.5	0.357	163.8±50.1	149.2±39.7	0.057	0.404
C24:1 (nervonic acid)	34.7±6.2	32.0±6.4	0.007	37.9±7.4	36.8±7.7	0.297	0.250
SCD-16 (C16:1/C16:0)	0.10±0.03	0.10±0.02	0.755	0.10±0.04	0.10±0.04	0.971	0.840
SCD-18 (C18:1n-9/C18:0)	2.97±0.61	3.12±0.77	0.195	2.97±0.44	3.07±0.53	0.151	0.685
D6D (C18:3n-6/C18:2n6)	0.012±0.005	0.013±0.007	0.023	0.012±0.007	0.012±0.005	0.917	0.365
D5D (C20:4n-6/C20:3n6)	5.70±1.88	4.75±1.31	0.001	5.30±2.24	4.90±1.37	0.253	0.199

Data are means±SD.
*p Value for the intragroup comparison (baseline vs 16 weeks).
†p Value for the intergroup comparison (change from baseline between groups).
D5D, Δ5 desaturase.

be related to the limitation that the observation period was too short to detect beneficial effects on lipid profiles or blood pressure. Sitagliptin-mediated and mitiglinide-mediated improvements in glycemic control were independent of the lipid profile or insulin secretion (see online supplementary table S2), suggesting that unique and as yet unrecognized mechanisms may underlie the actions. Indeed, insulin secretion during the arginine challenge and lipid meal tests decreased significantly in the sitagliptin group after the switch from insulin. The effects of glucagon-like peptide-1 on glucagon secretion, gastric emptying, and the autonomic nervous system may explain such an effect of sitagliptin.[30] In addition, our

results suggest that glinides also have a glucose-lowering effect independent of their effect on insulin secretion.

In contrast to a previous report,[31] DHA and EPA levels did not predict the sitagliptin-mediated improvement in glycemic control (see online supplementary table S2). In addition, this is the first study to demonstrate sitagliptin-mediated and mitiglinide-mediated changes in serum fatty acid profiles in humans or animals. Sitagliptin, but not mitiglinide, dynamically altered fatty acid composition; it increased serum levels of fatty acids, such as lauric acid, myristic acid, γ-linolenic acid, α-linolenic acid, eicosatrienoic acid, dihomo-γ-linolenic acid, and erucic acid. The effects of sitagliptin on fatty

Table 3 Changes in treatment satisfaction

	Sitagliptin			Mitiglinide			
	Before	After	p Value*	Before	After	p Value*	p Value†
Q1	4.1±1.7	4.9±1.1	0.057	4.3±0.3	4.8±0.3	0.197	0.620
Q2	3.1±1.4	2.6±1.7	0.264	2.6±0.3	2.9±0.4	0.412	0.170
Q3	2.3±1.9	1.9±1.9	0.358	1.3±0.2	1.9±0.4	0.166	0.110
Q4	3.7±1.7	5.2±0.9	0.000	3.0±0.4	5.0±0.3	0.000	0.268
Q5	3.7±1.3	4.7±1.3	0.006	3.1±0.4	4.8±0.3	0.000	0.146
Q6	4.1±1.3	4.6±1.0	0.043	4.6±0.2	4.5±0.3	0.887	0.154
Q7	4.3±1.5	5.0±0.8	0.013	3.7±0.4	4.4±0.3	0.052	0.931
Q8	4.1±1.6	5.1±1.0	0.002	3.7±0.4	4.8±0.3	0.008	1.000
Sum	24.2±6.7	29.6±4.5	0.000	22.3±1.6	28.4±1.3	0.001	0.759

Treatment satisfaction score: sum of items 1, 4, 5, 6, 7, and 8. Data are means±SD.
*p Value for the intragroup comparison (baseline vs 16 weeks).
†p Value for the intergroup comparison (change from baseline between groups).

acid profiles were independent of its effects on glycemic control, insulin sensitivity, and cardiovascular markers (data not shown). D5D and D6D catalyze the synthesis of long-chain n-6 and n-3 polyunsaturated fatty acids (PUFAs), and their activities can be estimated using PUFA product-to-precursor ratios.[32][33] The D5D activity index is negatively associated with insulin resistance,[33][34] onset of newly diagnosed type 2 diabetes,[32] and an adverse profile of several metabolic risk factors in patients with metabolic syndrome[35] in cross-sectional studies. Insulin activates D5D in patients with diabetes.[36] However, another cross-sectional study showed that patients with poorly controlled type 2 diabetes have a higher D5D activity index,[37] and improving glycemic control with intensive insulin therapy significantly decreases D5D in patients with type 2 diabetes.[38] Our study is the first to show the effect of a dipeptidyl peptidase-4 (DPP-4) inhibitor on D5D and D6D. After the switch from insulin, sitagliptin significantly decreased D5D, whereas it significantly increased D6D. Neither the baseline levels of D5D nor D6D predicted the sitagliptin-mediated improvement in glycemic control. Thus, sitagliptin, but not mitiglinide, may exert unique pleiotropic effects on fatty acid composition. The molecular mechanisms underlying the sitagliptin-mediated effects on fatty acid metabolism should be pursued in future studies.

Finally, patients who took sitagliptin or mitiglinide after switching from insulin ameliorated overall QOL as assessed by the DTSQ. The DTSQ was developed to enable respondents to evaluate their current treatment in relation to their previous treatment. Among the DTSQ subscale scores, convenience of treatment, flexibility of treatment, and satisfaction to continue current treatment showed a significant increase after switching from insulin in both groups. Previously, it was reported that less treatment satisfaction is related to insulin treatment.[39] In addition, the satisfaction with treatment is reported to significantly correlate with adherence.[40] Therefore, in this study, convenience of OHAs may contribute to satisfaction with treatment.

Patient factors associated with changes in HbA1c remain unclear after switching from a bolus insulin regimen to an OHA. Total insulin doses before switching from mealtime bolus insulin monotherapy to either sitagliptin or mitiglinide predicted changes in HbA1c in both groups. Interestingly, total insulin doses/body weight predicted changes in HbA1c only in the sitagliptin group, but not in the mitiglinide group, whereas body weights did so only in the mitiglinide group, but not in the sitagliptin group. This may be because the effect of mitiglinide, but not sitagliptin, is dependent on plasma drug concentration that is decreased in increased body weight.

The baseline CPI significantly predicted changes in HbA1c only in the sitagliptin group. One study reported that the CPI is associated with pancreatic β-cell function in Japanese patients with type 2 diabetes; patients with CPI<0.8 usually require insulin therapy.[41] Our study is the first to prospectively demonstrate usefulness of the CPI for "tailor-made" diabetic medicine. Patients with a CPI<1.4 had worse HbA1c levels after switching to sitagliptin.

Our study has some limitations. First, mealtime dosing of rapid-acting insulin analog monotherapy may be a less common regimen in the diabetes treatment strategy. However, we previously showed that approximately one-half of the Japanese patients with type 2 diabetes retain β-cell function enough to achieve appropriate control of FPG by rapid-acting insulin analog monotherapy.[1] We hypothesized that such patients may be considered switch to DPP-4 inhibitors or glinides. Second, it was unexpected that all the study participants experienced exacerbation in glycemic control after switching from bolus insulin regimen to OHAs. However, as a result, the potent effect of mealtime dosing of rapid-acting insulin analog monotherapy on glycemic control was confirmed in patients with type 2 diabetes. As we showed in this study, insulin doses and β-cell function may predict feasibility to sitagliptin therapy. Third, we intended to compare the efficacy of sitagliptin versus mitiglinide in controlling FPG after switching from

insulin therapy. Therefore, we designed a parallel group study just comparing these agents. However, setting the control group that continued the insulin therapy further enables one to compare the efficacy of bolus insulin and OHAs in controlling FPG and HbA1c.

In conclusion, nadir FPG and HbA1c were exacerbated in patients receiving sitagliptin or mitiglinide after switching from mealtime dosing of a rapid-acting insulin analog. Mean FPG increased significantly in the mitiglinide group, whereas it remained unchanged in the sitagliptin group, but participants achieved similar glycemic control after switching from the bolus insulin regimen. In contrast, switching to sitagliptin or mitiglinide decreased BMI and waist circumference and increased QOL. Sitagliptin, but not mitiglinide, may exert unique pleiotropic effects on fatty acid composition. Patients whose mean total daily doses of rapid-acting insulin analog were 16.6 and 17.8 units were switched to sitagliptin and mitiglinide, respectively, without a change in the HbA1c level. Additional therapy to sitagliptin or mitiglinide is clearly required to obtain equivalent glycemic control in patients using higher dosing of insulin.

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